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Curriculum: Philosophy of language and mind, psychology, and evolutionary sciences

Aging and neurodegenerative diseases:
Normative data of Mini Addenbrooke's Cognitive Examination (M-ACE) and a new version "M-ACE6" derived from the Mokken Scale Analysis

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Vita sana e ordinata, la dieta moderata, medicine quasi mai

E cerca, se ce la fai, di arrabbiarti poco o niente.

Ginnastica e le tue passioni, scorda le preoccupazioni

Aria aperta, tanti amici e in testa mille occupazioni

Roberto Abadie Soriano (1895-1992), scrittore

Alla mia famiglia

Ai miei zii

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INTRODUCTION

"*Dementia*" is an umbrella term encompassing neurodegenerative, progressive and chronic diseases characterised by multiple onsets, signs and symptoms. Worldwide estimates suggest that it is *a global emergency,* predicting an exponential increase in cases by 2050, to around 65 million.

This dissertation aims to examine the Italian normative data of the short-form of the Addenbrooke's Cognitive Examination-III (ACE-III), a screening test for global cognitive functioning. This test, which has already been validated in other countries, is known as the Mini-Addenbrooke's Cognitive Examination (M-ACE).

The proposal of new diagnostic tests, or different versions of existing tests, is in response to the need to update the tools to be used in a population that is undergoing constant change, both culturally and socially.

To illustrate this point, consider Mini-Mental State Examination (MMSE), a test of cognitive screening, developed in 1975; it is evident that, in comparison to 50 years ago, the target population has undergone substantial sociological, cultural, and technological changes. Consequently, this instrument should therefore be modified to ensure adequate discrimination between healthy individuals and those with dementia. A more detailed analysis reveals that the current level of educational attainment is significantly higher today compared to fifty years ago, a period during which women were not guaranteed access to

education and the average degree of education of the general population was comparatively low. On the other hand, test theory postulates that scores on cognitive assessments should be revised in light of societal changes, particularly with regard to gender and degree of education.

This research work is therefore driven by an aspiration to explore a pivotal domain crucial area of neuropsychology, with the objective of contributing to the advancement of knowledge not only on neurodegenerative diseases, but also on their assessment. An accurate assessment, supported by appropriate tools and a multidisciplinary approach, can indeed facilitate the early identification of cases and the planning of more effective treatments (Smith et al.2022). A well-structured assessment is also a fundamental support for the families involved, helping them to better understand the condition of vulnerability and suffering experienced by their loved ones. Indeed, research has a fundamental duty: ***"not to forget those who forget"***.

In this thesis, the first chapter provides a comprehensive overview of a physiological ageing, also known as "brain ageing", and the changes that affect cognitive functioning. Following and examination of "normal" ageing, the section advances to an analysis of "Subjective Cognitive Decline", an undiagnosable condition. It then delves into Mild Cognitive Impairment (MCI), and into dementias, highlighting their predominant etiological subtypes. In the opening chapter, an examination of the scientific literature about dementias is conducted, with a focus on their morphological and clinical characteristics.

Subsequently, a discussion is initiated on risk factors, defined as elements that enhance the probability of cognitive decline, although without determining its definitive onset.

The second chapter focuses on neuropsychological assessment and screening tests of global cognitive functioning, analysing the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) , in light of a thorough review of the relevant literature. These tests are considered *gold standards* in the field and they are therefore the most frequently cited in the literature and used in clinical and experimental studies. In the context of this thesis, studies on the Addenbrooke's Cognitive Examination (ACE-III) were also included to make the choice of validating a short version of it more explicit. The chapter then continues with a review of the scientific literature on the psychometric comparison of the above-mentioned tests.

The third chapter constitutes the empirical part of this study with its two aims. The chapter opens with the normative data of the short version of the Mini-Addenbrooke's Cognitive Examination (M-ACE), describing the limitations highlighted by the studies analysed and the modifications made to the original version of the test, including the addition or exclusion of some items. The first research aim was to validate the original version of the M-ACE in a population of healthy subjects, patients with MCI and patients with dementia. The starting hypothesis was that the M-ACE would have good psychometric qualities for discriminating between healthy patients and those with dementia, and that it

would be able to diagnose subjects with MCI; furthermore, the second hypothesis was that the M-ACE would have better diagnostic qualities than the MMSE in the sample. The results of the validation of M-ACE are then presented. Following the comparison between the M-ACE and the MMSE and the ACE-III.

The subsequent chapter of this study sets out to achieve the second aim of the research, which consists of proposing an alternative version of the M-ACE. This is to be proposed using the Mokken Scale Analysis (MSA), as suggested in the original validation by Hsieh et al. (2015). The rationale underlying the exploration of a new scale stems from the assumption that, although the M-ACE has been validated in other countries, it has not been validated in Italy. Indeed, the hypothesis was that, given the cultural differences between countries, we would find different discriminating items compared to the M-ACE. The analysis resulted in the development of a new version, the M-ACE6.

Specific statistical analyses were conducted to assess its psychometric properties and its potential future applicability. For example, the ROC curve was used to evaluate the performance of a binary classification model by obtaining the true positive and false positive rates. The ROC curve also allows us to understand how well the model discriminates between the two classes. Logistic regression analyses were used to verify the probability of having dementia according to the predators found. Non-parametric analyses were

performed to explore sample size and the non-causal relationship between variables.

The section then concludes with a discussion of the results and a concluding paragraph summarizing the main findings.

Section 1

Aging and neurodegenerative diseases

1. Aging

The increase in human life expectancy over successive generations can be attributed to the evolutionary trajectory of the species, as well as to environmental changes, general improvements in living conditions, and advancements in medical care. These developments have contributed to an increase in both the length and quality of life (Flatt & Plattridge, 2018).

The ageing phase is defined as a physiological process characterised by changes that are perceived by the individual and affect biological, psychophysical and psychosocial functioning (Baltes, 1987; Park & Reuter-Lorenz, 2009; Dziechciaz & Filip, 2014). The biological changes attributable to ageing are the result of a network formed by genetic and/or hereditary factors, environmental factors, and lifestyle choices that either contribute to or preserve the elderly from possible chronic diseases. According to the World Health Organization (WHO), ageing is defined as the process of developing and maintaining functional capacities that enable well-being in old age (World Report on Ageing and Health, 2015). At this stage of the life cycle, the concept of

“functional capacity” refers to the ability to meet one's needs, learn, make decisions, maintain independence and autonomy, build and maintain relationships, and contribute to society; these abilities are the product of an individual's internal awareness confirmed or not by feedback from the environmental context (Michel & Sadana, 2017; Fallon & Karlawish, 2019; Rudnicka, Napierała, Podfigurna, Męczekalski, Smolarczyk & Grymowicz, 2020). The process of ageing has been, and continues to be, the subject of extensive research, with numerous theories attempting to explain its characteristics, changes, and the psychological and experiential experience of the elderly. For instance, Erickson's (1950) theory of the eight stages of development introduces the phase of ageing characterised by profound reflection on the meaning of life and a search for fulfilment. The "Selection, Optimisation and Compensation - SOC Theory" of Baltes (2003) conceptualizes ageing as a phase characterised by the significance of emotional wellbeing, social relationships and positivity, given the individual's awareness of reaching the final stage of life. This theory suggests that the outcome is a preference for maintaining a high quality of life and a reduction in negative experiences.

In 2009, Levy examined the impact of stereotypes on ageing, highlighting how these stereotypes can influence the emotional and behavioral domains. The author then explored how stereotypes can be internalized by the elderly, leading to alterations in their self-perception. Within the framework of the “Stereotype Embodiment Theory”, Levy emphasised the prevailing belief that the elderly

are often perceived as forgetful, confused, and less able to act. The theory also acknowledges the existence of positive stereotypes that, conversely, can have a beneficial effect on the elderly, engendering feelings of wisdom and experience. In summary, the process of ageing, as a phase of the life cycle, is characterised by evolutionary changes that affect the physical, psychological and social spheres in a manner analogous to the other phases already experienced.

1.1 Epidemiological data on the elderly population in the world and in Italy

According to data reported by the WHO in 2015, between 2015 and 2050, the number of people aged 80 years or older would rise to around 426 million, while the percentage of the global population aged 60 years or older is expected to gradually increase over time by 22% to around two billion (World Report on Ageing and Health, 2015). According to forecasts dating back to 2022, the WHO has predicted that *"by 2030, 1 in 6 people worldwide will be 60 years of age or older. The share of this population will increase from 1 billion in 2020 to 1.4 billion. By 2050, the population aged 60 and over will double to about 2.1 billion".* On 10 January 2024, Eurostat estimated the elderly population to be around 449 million, with an average of 44.7 years. Italy has the highest average age in Europe (48.7) (Figure 1). The ISTAT report of 2023 documented

an increase in the population over the age of 65 to approximately 14.177 million individuals, constituting 24.1 % of the Italian population of which, 7.7 % were individuals over 80 years of age.[1]

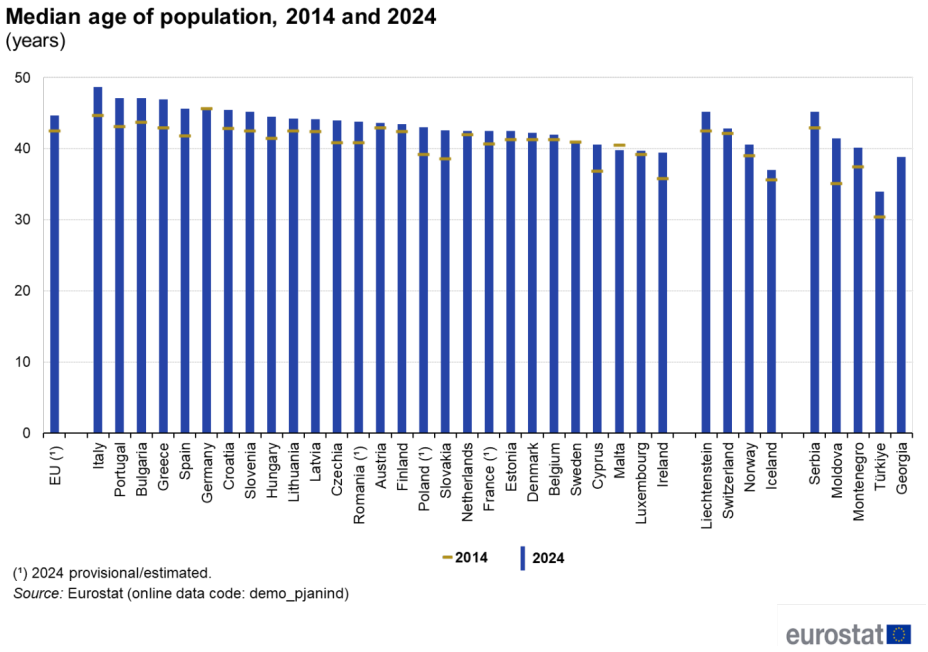


Figure 1- Media age of population in Europe

1.1.2 Synaptic plasticity and anatomo-structural changes in ageing

The concept of synaptic plasticity refers to the phenomenon of change, in terms of either consolidation or reduction, in the strength of the synaptic bond

[1]Source:https://ec.europa.eu/eurostat/statisticsexplained/index.php?title=Population_structure_and_ageing&action=statexp-seat&lang=it; https://www.istat.it/storage/rapporto-annuale/2023/Rapporto-Annuale-2023.pdf

between nerve cells. This change occurs predominantly at the level of the cerebral cortex (Berlucchi & Buchtel, 2009). In 1949, the psychologist Donald Hebb made a significant contribution to the field of synaptic plasticity by introducing the concept of *Hebbian learning*, which emphasized the neural mechanisms of memory and learning: if a pre-synaptic neuron "A" and a post-synaptic neuron "B" are activated simultaneously and repeatedly, their synaptic bond will change, acquiring greater strength. This mechanism was later confirmed by the discovery of the concepts of **long-term potentiation** (LTP) and **long-term depression** (LTD). LTP, predominantly located in specific areas of the central nervous system, including the hippocampus, refers to synaptic bonding in which the stimulus is present in rapid succession and at high frequency; LTD phenomena are characterised by low-frequency stimuli that result a reduction of synaptic strength. While LTP reinforces the link between nerve cells, LTD facilitates the suppression of synaptic bonds that are superfluous to the function of the brain. Aging is associated with alterations in these mechanisms, especially in the hippocampal region, which can result in impaired learning and memory (Leal & Yassa, 2015; Chen, Farrell, Rundle, Chan, Moore, Wig & Park, 2021).

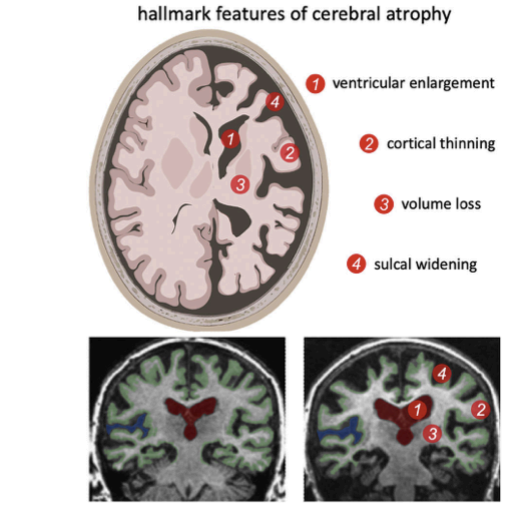
Until a few decades ago, age-related cognitive impairment was considered a consequence of neuronal death. Synaptic plasticity phenomena were only attributed to the developmental and adolescent age. However, scientific research has provided evidence that the mature brain is subject to plasticity

phenomena involving structural changes, such as the growth or retraction of dendritic spines, the strengthening of synaptic transmission and the formation of new synapses (Yuste & Bonhoffer, 2001).

Regarding the brain changes that occur in the ageing phase, the use of *brain imaging* techniques, such as computed axial tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), has made it possible to detect a reduction in the number of neurons, brain volume and weight (*brain atrophy*), dilation of the ventricles, and a flattening of the cerebral circumvolutions (figure 2). Atrophy and reduced synaptic connectivity are associated with an inevitable functional change in neurotransmitter circuits involving acetylcholine, serotonin, catecholamines and GABA. There is also an increase in neurofibrillary tangles of tau protein, neuritic plaques (aggregates of Aβ-amyloid protein) and glial cells, which are responsible for protecting nerve cells but which, if present in greater numbers, do not fulfil their original function. Furthermore, age-related white matter flaking can result from axonal degeneration, myelin changes or glial cell malfunctioning and accumulation of cellular debris (figure 3) (Fjell & Walhovd, 2010; Pannese, 2011; Juraska & Lowry, 2012; Bennett & Madden, 2014; Ritchie, Tisdall, Quereshi, Buckner, van der Kouwe & Fischl, 2015; Damoiseaux, 2017)

The described changes are not uniformly present in all areas of the brain (figure 4); for instance, the lower number of neurons and synapses predominantly affects the prefrontal and temporal cortex, hippocampus and locus coeruleus

Harley, 2016 (Burke & Barnes, 2006; Morrison & Baxter, 2012; Mather & Barnes, 2006; Morrison & Baxter, 2012; Mather & Harley, 2016) while in a longitudinal study, cortical thickness showed a decrease in the regions parahippocampal , temporal lobes and entorhinal cortex (Sele, Liem, Mèrillat & Jancke, 2021).



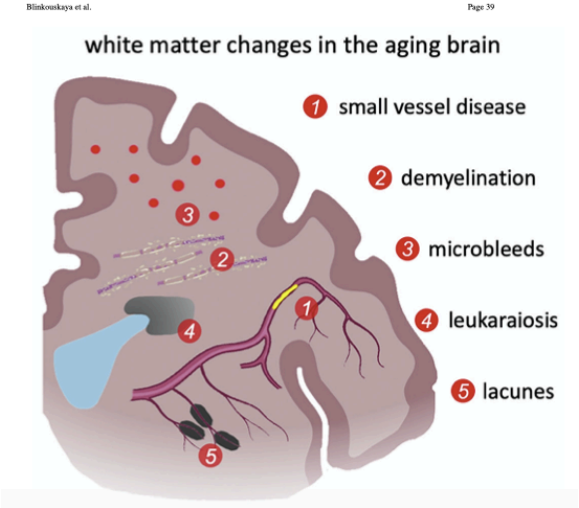


Figura 2. Brain Atrophy

Figura 3. Changes in white matter in the aging brain

Source: Blinkouskaya, Y., Caçoilo, A., Gollamudi, T., Jalalian, S., & Weickenmeier, J. (2021). Brain aging mechanisms with mechanical manifestations. *Mechanisms of ageing and development*, *200*, 111575.

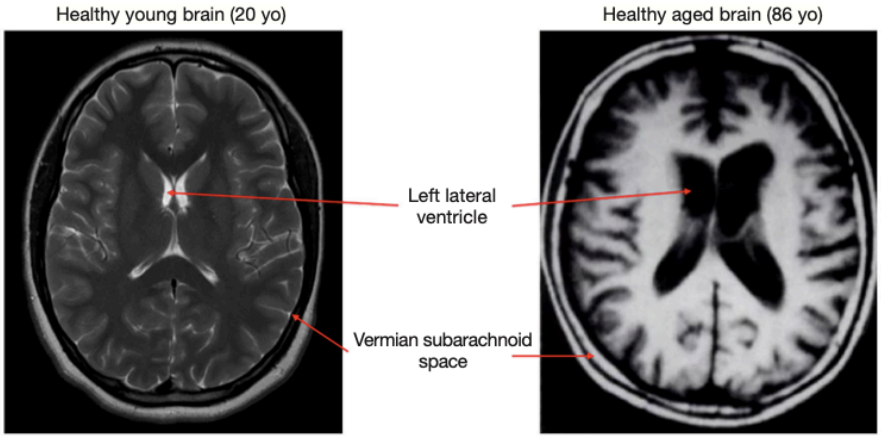


Figura 4. Anatomical and structural changes in the mature brain (right). Source: Humayun, H., & Yao, J. (2019). Imaging the aged brain: pertinence and methods. *Quantitative Imaging in Medicine and Surgery*, *9*(5), 842.

1.1.3 The hippocampus

The scientific literature has provided rich evidence of the involvement of the hippocampus and its modifications in ageing.

The hippocampus is a small portion of the temporal lobe, bilaterally arranged and belongs to the limbic system. Its function in episodic and spatial mnemonic processes learning and the regulation of emotional behavior, has made this portion an important object of study underlying cognitive functioning in the elderly and neurodegenerative diseases. The hippocampus is the site of the highest concentration of receptors for *Brain-derived Neurotrophic* Factor (BDNF), a neurotrophic and growth factor that regulates synaptic plasticity in

both the central nervous system (CNS) and the peripheral nervous system (PNS) (Barde & Edgar, 1982). BDNF has a protective effect on neurons and plays a role in memory and learning processes. During the process of ageing, a decline in BDNF release can be attributed to neuro-inflammatory processes that contribute to reduced neurogenesis and synaptic connectivity, thereby limiting nerve cell function in the hippocampal area (Bartsch & Wullf, 2015; Bettio, Rajendran & Gil-Mohapel, 2017). Other changes at the cellular level, such as oxidative stress and increased glucocorticoids, which are supported by an alteration of the hypothalamic-pituitary-adrenal axis (HPA), involve the processes of neuroinflammation and decreased neurogenesis in the hippocampal area, rendering this area particularly vulnerable to ageing (Lucassen, Pruessner, Sousa, Almeida, Van Dam, Rajkowska et al., 2014).

Furthermore, a number of theories have been concerned with defining the role of the hippocampus in the processes of encoding, processing and storing material to be memorised. According to "**Multiple Trace Theory**" (Winocour, Moscovitch & Sekeres, 2007), activation of the hippocampus is a prerequisite for the retrieval of information from long-term memory. Instead, the **"Trace Consolidation Theory**" (Squire, 2009), asserts that the hippocampus plays a key role in the consolidation of stimuli, though not in their retrieval. The Multiple Trace Theory has thus far been most useful in explaining memory deficits related to the retrieval of both recent and remote memories. This has

enabled researchers to define the role of the hippocampus in the healthy and pathological functioning of memory processes.

1.2 Aging: what changes in cognitive functioning?

Physiological cerebral ageing is accompanied by a gradual decline in cognitive functions, which does not affect the subject's functional capacity or autonomy. The following section will examine the main changes occurring in the ageing phase.

Memory: During ageing the most evident impairment concerns about this multi-componential domain, located in the parieto-temporal areas of the cortex. Memory is the capacity to encode, store and retrieve information, and it is generally distinguished into three main components: a sensory store, a short-term store (MBT), working memory (WM) and a long-term store (MLT). While Atkinson and Shiffrin (1968) initially described a multistage model involving MBT, MLT and sensory memory, subsequent research has introduced more complex models that offer a more comprehensive understanding of the human memory system.

Sensory memory is responsible for the rapid encoding of visual, auditory, olfactory, and gustatory stimuli for the duration of a few seconds. Due to ageing, sensory dysfunctions may be present, e.g., in the visual and auditory capacity, which affect the ability to encode and thus store stimuli less accurately (Hong et al., 2024). The **MBT** has been shown to process and store new material, with a limited capacity of 7 ± 2 units (Miller, 1956) for approximately 20 seconds (Peterson & Peterson, 1959). In the context of the elderly population, studies have demonstrated that there are no substantial changes in this life stage when tasks require the retention of information (Parkin & Walter, 1991; Wahlin et al., 1995; Gregoire et al., 1997). The capacity-constrained system involved in the processing, simultaneous updating and retrieval of information is the **working memory** (Baddeley & Hitc,1994; Baddeley, 1998; Kirova, Bays & Lagalwar, 2015). This system is characterised by a *central executive* that controls the visuospatial, *sketchpad*, responsible for the processing of information and the *phonological loop,* responsible for the retention and processing of verbal information. Later, Baddeley (2003) proposed the concept of the *episodic buffer*, a component that plays a temporary role in integrating information from different storage modalities (sensory memory, short-term memory, long-term memory). A review of extant literature reveals a vulnerability of working memory to the effects of advancing age. Attention and executive functioning are involved in working memory and they are certainly vulnerable to ageing (Verhaeghen et al. 2019; Holcomb et al., 2022). However, the underlying mechanisms that render this vulnerability

remain contentious. The **MLT** is the store in which long-term memories are deposited and it includes explicit or declarative memory in which we recognize **episodic memory** (Tulving, 1986), the process of unconsciously, which relates to recent facts concerning experiences to which the individual is exposed, and **semantic memory** (Tulving, 1986), which contains general knowledge consolidated over time. In the long-term store, we also distinguish **autobiographical memory** (Williams et al., 2008), which recovers personal life events and includes the subjective reenactment of the event, characterised by the activation of the amygdala for emotional processing. Autobiographical memory includes both episodic memory, which allows us to recollection of events to which an individual has been exposed (e.g. what we did the day before), and semantic memory, i.e. all stored knowledge (e.g. the whale is a mammal), are involved. Finally, about the long-term store, **prospective memory** (Craik,1986; Einstein & McDaniel,1990), is devoted to remembering tasks to be performed in the future. MLT is linked to the functions of retrieval, recognition and retention of material and resists changes due to for ageing longer. The greatest evidence of difficulties in MLT concerns episodic memory due to brain morphological changes in the temporal areas, prefrontal cortex and hippocampus during the ageing phase. Indeed, there is a decline in episodic memory and also a slowdown in working abilities memory; these results are reflected in an individual's difficulty to remember even recent life events (Balota, Dolan & Duchek, 2000; Kliegel, Ballhaunsen, Hering, Ihle, Schnitzspahn & Zuber, 2016). Autobiographical memory, which is linked to

episodic memory, may also be slowed down, activating both hippocampal areas in elderly people, whereas in younger people, remembering personal events only activates the left hippocampus (Allen, et al., 2018). The efficiency of episodic memory depends on the individual's cognitive reserve; indeed, loss of this part of memory is not common in the elderly (Friedman et al., 2013). Prospective memory performance in the elderly has been shown to be inferior to that of younger individuals for routine activities and spontaneous retrieval (Uttl, 2008; Kliegel et al., 2016). The long-term store, comprising semantic memory and procedural memory, has been found to demonstrate greater resilience to the effects of ageing (Balota et al., 2000). In the context of procedural memory tasks, such as priming tasks, elderly individuals demonstrate a performance level comparable to that of young adults (Zacks et al., 2000); the consolidation of long-term traces of semantic memory and their resistance to ageing, on the other hand, calls into question the importance of cognitive reserve (Backman & Nilsson, 1996).

Memory, as a multi-componential system, involves multiple brain areas underlying a neural network. Thinking of memory as an “isolated” cognitive domain is not possible. Indeed, memory involves the integrity of other cognitive functions, such as attentional capacity, processing speed, executive functioning, and perception (Squire & Wixted, 2011).

Executive Functions: Executive functions, located in the frontal and prefrontal areas of the neocortex, are defines as higher-order abilities necessary for the

performance of complex cognitive processes such as planning, organisation, cognitive flexibility, decision-making and goal-oriented behaviour (Burgess, 1997; Spreen & Strauss, 1998). Executive functions represent a set of skills that involve the inhibition of responses, switching between mental representations, updating working memory representations, involving attentional processes, and reasoning (Miyake, Friedman, Emerson, Witzki, Howerter & Wager, 2000). The "***Frontal lobe hypothesis of ageing***" (Dempster, 1992) explains the atrophy of the prefrontal cortex and the alteration in executive functioning in elderly who show less capacity for inhibitory responses, i.e. less capacity to select an appropriate response to a stimulus, a slower processing speed and less shifting capacity, i.e. less capacity to move from one task to another (Dempster 1992; West, 1996). These findings are confirmed by a recent exploratory study (Idowu & Szameitat, 2023): in a series of tasks assessing executive functions, the elderly obtained lower scores than adults, especially in inhibition tasks (e.g. tasks in which the subject is asked to inhibit a behaviour, such as go/no go, Stroop test) confirming data already present in the literature (Maldonando et al., 2020).

Attention: Attention is a cognitive function that underlies various cognitive processes and involves different brain areas, such as the parietal cortex, prefrontal cortex, cingulate cortex, and basal ganglia (Fabio et al., 2019). [2]

[2] For a comprehensive review, recommend reading Fabio, R. A., Caprì, T., & Towey, G. E. (2019). The neural basis of attention. *Attention Today; Caprì, T., Fabio, RA, Towey, GE, Antonietti, A., Eds*, 85-122.

Attentional processes involve the ability to select a stimulus in the environment, ignoring irrelevant information (**selective attention**); the ability to sustain attention for a prolonged time (**sustained attention**); the capacity to attend to two different stimuli concurrently (**divided attention**); the ability to shift between one stimulus and another (**alternating attention**) (Ladàvas, 2012). Attention and response times to stimuli are sensitive to the effects of ageing, given that the capacity for inhibition and shifting is involved in these processes based on sharing a cortical site: the prefrontal cortex. However, it would seem that in selective and sustained attention tasks, elderly subjects perform better on trials, but differ in terms of older age, motivation and task difficulty (Van Gerven & Guerreiro, 2016; Zanto & Gazzaley, 2019).

Moreover, in the review of Verissimo et al., (2022), an examination was conducted of a number of studies related to the theory proposed by Posner and Petersen in 2012. According to this theory, there are three primary attentional networks: the **Orientation Network**, which is responsible for orienting attention towards objects or events in the environment; the **Executive Network**, which demands greater levels of concentration and self-control; the **Vigilance Network**, which is associated with the ability to maintain attention in a state of constant vigilance. In accordance with this theory, the results of review demonstrated that age-related changes are not uniform: during ageing, both the Vigilance Network and the Orientation Network may decline, while the Executive Network would demonstrate improvement in performing such tasks. In everyday decision-making processes, this heterogeneity can be

attributed to the lived experience and practical knowledge acquired by the elderly. This heterogeneity is partly due to individual factors, including education and cognitive reserve, as well as to the brain localization sites of the Networks involved, such as the prefrontal and frontal cortex, and the parietal lobes.

Language: language production is characterised by slowdowns related to language processing are evident during the ageing phase. Although vocabulary is preserved in the elderly (Whiting et al., 2003), difficulties in word-finding are evident during both spontaneous speech and in tasks that require the production of specific words, such as in verbal and semantic fluency tasks or naming tasks (Shafto & Tyler, 2014). Indeed, the typical increases in “tip-of-the-tongue" (TOT) frequency characterised by the feeling of having the word "on the tip of the tongue" yet being unable to recall it, is not necessarily indicative of impaired access to the lexicon and semantics (for a thorough review see Shafto et al. 2007). In general, syntactic complexity is not significantly enriched which periods potentially containing supplementary information to explain concepts, likely attributable to the loss of the inhibitory capacity of executive functions (Wright, 2016). Regarding language comprehension, this does not appear to be influenced by ageing, with the exception of the difficulties in understanding abstract concepts or syntactically complex sentences (Shafto & Tyler, 2014). Once more, the efficiency of this

cognitive function depends on both the underlying biological mechanisms and individual experience.

Intelligence - Empirical studies in the literature confirm the relationship between the characteristics of certain structures brain and intellectual abilities (Pietschnig, Penke, Wicherts, Zailer & Voracek, 2015). Jancke et al. (2020) investigated the relationship between grey matter volume and results on a series of psychometric tests on verbal and non-verbal intelligence. The results from a sample of 231 healthy elderly people, observed and evaluated over a period of 4 years, showed a reduction in certain brain areas, but not impairing performance on intelligence tests. With regard to theories on intelligence in the ageing phase, reference is made to the model of fluid and crystallized intelligence[3] by R. Cattell (1943; 1963), whereby acquired knowledge accumulated during the course of life, appears to be more conserved in ageing than those functions attributable to fluid intelligence (e.g., skills such as reasoning, problem solving, processing of previously unlearnt information). Consequently, with ageing, there is therefore a gradual decline in the abilities attributable to fluid intelligence, which are dependent on processes of stimulus processing speed, the working memory, attention and perceptual speed, i.e., the speed with which we process stimuli perceived in the environment (Salthouse,

[3] **Fluid intelligence** is the ability to solve new problems, adapt to unexpected situations and think flexibly, without relying on prior knowledge. It is associated with the capacity for abstract reasoning and logical thinking. **Crystallised intelligence**, on the other hand, is the body of knowledge acquired through experience and learning, such as vocabulary, cultural information and practical skills. It grows with age and experience, and is more stable over time than fluid intelligence.

2010; 2019; Hertzog, 2020). Finally, the paucity of studies on reasoning and problem-solving in the elderly, that would include both fluid and crystallized abilities (Cohen, Marsiske & Smith, 2019), renders findings unclear and ambiguous.

1.3 How does ageing become pathological?

The previous section briefly outlined the characteristics of specific cognitive functions in older people. Many studies have been interested in changes during the life cycle to identify possible prevention and treatment strategies. As with other physiological aspects, cognitive functions change with advancing age.

The demographic growth of the world's elderly population makes it statistically predictable that age-related diseases (including the development of neurodegenerative processes) will increase.

Dementia is a progressive and chronic neurodegenerative disease for which age is a well- established risk factor. A study (Nichols, Steinmetz, Vollset, Fukutaki, Chalèk, Abd-Allah et al., 2022) estimates that the number of people with dementia worldwide will increase from 57 million in 2019 to about 150 million in 2050, with 74% of cases are expected to occur in Western Europe (World Health Organization, 2021). In Italy, the total number of people with dementia is over 1 million, including 600,000 people with Alzheimer's disease

(AD), one of the etiological subtypes of dementia[4]. The forms of cognitive decline are described below.

1.3.1 Subjective Cognitive Decline (SCD) and Mild Cognitive Impairment (MCI)

SCD is the stage in which the individual perceives a change in cognitive performance that is likely to be age-related; a stage in which relevant neurological signs and cognitive and/or behavioral symptoms are not present. The perceived loss may affect any cognitive domain and may remain stable or worsen over time (Lin, Shan, Jiang, Sheng & Ma, 2019).

SCD may represent a stage prior to the development of dementia, making it an excellent starting point for early diagnosis. A diagnosis of SCD is not clinically applicable, but individuals who recognize this stage may be more likely to experience cognitive decline than those without such symptoms. However, several medical conditions can cause SCD and data in the literature suggest that it cannot be considered a certain indicator of future cognitive decline, but a condition that needs to be more clinically assessed as it could be a risk factor (Jessen, Amariglio, Buckley, van der Flier, Han, Molinuevo et al, 2020; Jack, Bennett, Blennow, Carillo, Dunn, Haeberlein et al, 2018). In addition, studies have been conducted on characteristics related to personality and cognitive

[4] Source: https://www.istat.it/storage/rapporto-annuale/2023/Rapporto-Annuale-2023.pdf

processes that may be useful in discriminating SCD. Indeed, individuals with SCD would tend to have low energy and little activity, both physical and mental, which is associated with depressive symptoms (Munoz, Gomà-i-Freixanet, Rodriguez-Gomez, Sanabria, Pérez-Cordon et al., 2020; Wilson, 2023). In addition, poorer performance in metacognitive skills has been associated with lower scores on cognitive tests and comorbidity with anxiety and depressive symptoms (Jenkins, Tree, & Tales, 2021). These studies provide useful future research targets for prevention.

In contrast to cases of SCD, the presence of neurological signs and cognitive and/or behavioral symptoms can be assessed in cases of mild cognitive impairment.

The term Mild Cognitive Impairment (MCI) was first introduced in 1999 to describe an intermediate stage between physiological ageing and dementia (Petersen, Smith, Waring, Ivnik, Tangalos & Kokmen 1999). MCI is a stage of mild cognitive impairment in which autonomy and performance of normal activities of daily living are maintained, but the individual and/or family members report impairment in memory or another cognitive domain. Careful clinical assessment, supported by neuropsychological assessment, reveals a symptom framework somewhere between cognitive unimpairment (CU) and dementia. The most obvious reported impairment relates to memory function, but a careful diagnostic assessment may reveal other impairments in other domains (Albert, Dekosky, Dickson, Dubois, Feldman, Fox et al., 2011; Tangalos & Petersen, 2018). In Italy, according to the Istituto Superiore di

Sanità (2019), there are 900 thousand people with this symptomatology, with an incidence of 21.5% per 1000 people and a conversion rate from MCI to AD of 68.8% (Bianchetti, Ferrara, Padovani, Scarpini, Trabucchi & Maggi, 2019).

It is important to identify criteria for the clinical and cognitive syndrome of MCI, as the difference between normal cognition and MCI, and between MCI and dementia, is complex. The working group established by the National Institute on Aging and the Alzheimer's Association (Jack, Albert, Knopman, McKhann, Sperling, Carrillo et al., 2011) defines the following diagnostic criteria for clinical practice:

Concern on the part of the individual or a reliable informant about cognitive efficiency being impaired compared to a previous period;

1- Impairment demonstrated by neuropsychological assessment in one or more cognitive domains;
2- Functional autonomies preserved;
3- The impairment does not interfere with the individual's work or social functioning;
4- Exclude that MCI is secondary to other neurological pathology (cranial trauma, neoplasms, etc.);

The classification of the Manual Diagnostic and Statistical of Mental Disorders (DSM-5) (2014) defines it as "*mild neurocognitive disorder"*.

The diagnostic criteria are as follows:

- Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains such as complex attention, executive functions, learning and memory, language, perceptual-motor function or social cognition) based on:
- Concern of the individual, a reliable informant or the clinician that there has been a slight decline in cognitive function;
- A modest impairment of cognitive performance, preferably documented by standardised neuropsychological tests or, in their absence, by another clinical assessment;

a) Cognitive deficits do not interfere with independence in daily activities;

b) Cognitive deficits do not occur exclusively in the context of delirium;

c) Cognitive deficits are not better explained by another mental disorder;

Furthermore, it must be specified:

a) whether due to which aetiological subtype;

b) whether the cognitive impairment is accompanied by behavioural or non-behavioural impairment

The scientific literature defines the diagnosis of MCI as one of the risk factors for the future development of dementia. Studies in the literature have shown that structural changes (reduced hippocampal volume and atrophy in the entorhinal cortex) and genetic characteristics predict progression from MCI to neurodegenerative disease (Jack, Petersen, Xu, O'Brien, Smith, Ivnik et al, 1999; Devanand, Pradhaban, Liu, Khandji, De Santi, Segal et al, 2007;

Devanand, Bansal, Liu, Hao, Pradhaban & Peterson, 2012; Campbell, Unverzagt, LaMantia, Khan & Boustani, 2013). The recognition of MCI as a possible precursor to dementia has necessitated an evolution in diagnostic criteria, which have been revised and organised according to the domains affected. A distinction is made between amnestic MCI (aMCI) and non-amnestic MCI (naMCI), with impairments in multiple or single cognitive domains. aMCI is characterised by memory loss associated with a significant risk of progression to AD (Winblad, Palmer, Kivipelto, Jelic, Fratiglioni, Wahlund et al., 2004; Roberts & Knopman, 2013).

Although cognitive impairment is the main clinical criterion, behavioral and psychological disturbances may be an important feature of clinical presentation. Depression and apathy, agitation, anxiety, and irritability can be considered as characteristic symptoms of MCI compared to healthy individuals (Di Nuovo & Vianello, 2013; Kasper, Bancher, Eckert, Forstl, Frolich, Hort et al., 2020). Furthermore, patients with depressive symptoms and/or apathy show rapid cognitive decline and a high rate of conversion to dementia (Lee, Lu, Hua, Lee, Wu, Nguyen et al., 2012; Funes, Lavretsky, Ercoli, Cyr & Siddarth, 2018; Tan, Kohler, Hamel, Munoz-Sanchez, Verhev & Ramakers, 2019; Ma, 2020). Factors influencing the conversion of MCI to dementia are being investigated: age seems to be the most influential factor, deteriorating attention, vascular factors, the quality of cognitive reserve consisting of lifelong learning, reduced hippocampal volume and the presence of amyloid biomarkers in the cerebrospinal fluid suggest a higher likelihood of conversion to dementia

(Dubois, Hampel, Feldman, Scheltens, Aisen, Andireu et al, 2016; Khan, Giampietro, Banaschewski, Barker, Bokde, Buchel et al, 2017; Hu, Wang, Zhao, Zhu, Tian & Quin, 2021; McGrattan, Pakpahan, Siervo, Mohan, Reidpath, Prina et al, 2022).

However, there is a possibility that mild cognitive impairment may remain stable without progressing to dementia. It has been found that 40% of people with MCI stabilize at this stage, but it is also estimated that 10-15% of people with MCI will progress to dementia (Hu,Wang, Zhao, Zhu, Tian & Quin, 2021; Alzheimer's Association, 2022).

The risk factors for MCI are the same as those that contribute to the development of dementia. Genetic predisposition, environmental and lifestyle factors, other medical conditions such as diabetes, hypertension, dyslipidemia, smoking, obesity, the presence of depressive and/or anxiety symptoms, sedentary lifestyle, sleep disorders, vascular lesions, and low cognitive, physical and social activity increase the risk of developing MCI (Alzheimer's Association, 2022). However, the possibility exists that mild cognitive impairment remains stable without progressing into dementia. It is found that 40% of patients with MCI stabilise at this stage, but it is estimated that also 10%-15% of individuals with MCI will progress to dementia (Hu,Wang, Zhao, Zhu, Tian & Quin, 2021; Alzheimer's Association, 2022).

1.3.2 Dementias

Projections of the world's population by 2050 show a high proportion of people with dementia, partly due to the demographics of the world's population and increasing age changes (World Health Organisation, 2021). The number of people with dementia is estimated to be around 55-57 million, with a prevalence of 14 million in Europe alone (World Health Organization, 2015; Lopez & Kuller,2019; Nichols, Steinmetz, Vollset, Fukutaki, Chalèk, Abd-Allah et al., 2022). "*Dementia*" is an umbrella term describing a heterogeneous group of age-related cognitive symptoms characterised by progressive impairment of cognitive function caused by neurodegeneration of brain cells and resources (Tiepolt, Patt, Aghakhanyan, Meyer, Hesse, Barthel & Sabri, 2019). From an epigenetic perspective, changes in the transcription of neuronal genes that influence the occurrence of neurodegenerative processes have been identified and may represent targets for prevention and treatment (Hwang, Aromolaran & Zukin, 2017). Dementia is a pathological form of ageing that is highly critical for the life of the individual. Not one, but several risk factors make the individual vulnerable to this pathology. Age, gender, especially female gender, family history, low level of education, depressive symptoms, head trauma, vascular (hypertension, dyslipidaemia, diabetes) and cerebrovascular disorders, alcohol consumption, smoking and other lifestyle factors seem to favour the progression of the neurodegenerative process (Niccoli & Partridge, 2012; Durazzo, Mattsson, Weiner & Alzheimer's disease neuroimaging initiative,

2014; Tadic, Cuspidi & Hering, 2016; Biessels & Despa, 2018; Canet, Chevallier, Zussy, Desrumoux, & Givalois, 2018; Legdeur, van der Lee, de Wilde, van der Lei, Muller, Maier et al. , 2019; Gauthier, Rosa-Neto, Morais & Webster, 2021). These factors contribute to a significant inhibition of cellular activity in different brain regions, particularly affecting hippocampal regions, prefrontal and temporal lobes, which are cortices already associated with age-related changes (Liu, Yu, Wang,Han, Tan, Wang et al., 2015; Wang, Yuan, Pang, Ma, Han, Geng et al., 2016; Haller, Montadon, Rodriguez, Garibotto, Liljia, Hermann et al. 2019).

The most common form of dementia is Alzheimer's disease, but it is not the only one. Various etiological subtypes have been studied, such as mixed dementia, vascular disease, frontal-temporal degeneration and its subtypes, Lewy body dementia, Parkinson's disease and Corticobasal forms. The criteria for diagnosing dementia have evolved over the years and require the support of both brain imaging techniques and an accurate medical history, including neuropsychological assessment that takes into account the many psychometric instruments specific to different cognitive functions and the assessment of global cognitive function to analyse each case on a case-by-case basis. Both the biomarkers and the clinical signs present on the term dementia is still used today, both in the scientific literature and in the National Institute of Aging criteria (Jack, Bennett, Blennow, Carrillo, Dunn, Haeberlein et al, 2018); however, the DSM-5 has coined the term 'major neurocognitive disorder.

The diagnostic criteria **DSM-5** for major neurocognitive disorders are as follows:

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains based on:

1. Concern of the individual, a reliable informant or the clinician that there has been a significant decline in cognitive function;
2. A significant impairment of cognitive performance, preferably documented by standardised neuropsychological tests or, in their absence, by another quantified clinical assessment;

B. Cognitive deficits interfere with independence in daily activities;

C. Cognitive deficits do not occur exclusively in the context of delirium;

D. Cognitive deficits are not better explained by another mental disorder;

Furthermore, it must be specified:

a) whether due to any aetiological subtype;

b) whether the cognitive impairment is accompanied by behavioural impairment or not;

c) what is the current severity: mild, if the difficulties concern instrumental activities of daily living such as managing money; moderate, if the difficulties concern basic activities of daily living such as eating or dressing; severe, if the individual has completely lost his or her autonomy.

Neurocognitive (NCD disorder) involves the clinically acquired impairment of cognitive abilities: in major NCD the impairment is significant enough to spill

over into the patient's daily life, a condition that does not exist when mild NCD is diagnosed.

The aetiological subtypes are:

a) DNC due to Alzheimer's disease;

b) DNC due to degenerationfronto-temporal ;

c) DNC with Lewy bodies;

d) DNC due to vascular disease;

e) DNC due to head injury;

f) Substance/drug-induced DNC;

g) DNC due to HIV infection;

h) DNC due to prion diseases;

i) DNC due to Parkinson's disease;

j) DNC due to Huntington's disease;

k) DNC due to another medical condition;

l) DNC due to multiple aetiologies;

m) DNC without specification;

The symptomatic onset of neurodegenerative diseases is not common to all forms. It is important to emphasize the subjectivity of the course of the disease, which does not follow standardized stages, but depends on genetic predisposition, environmental factors, the person's cognitive reserve and life

circumstances in general. The most common forms of dementia characterised by cognitive impairment as the primary symptom are listed below.

1.3.3 Etiological subtypes

A review from 2014 to 2021 examined the epidemiology of Alzheimer's disease in Europe, Asia, and North America. The prevalence of cases is increasing, and in Europe in particular, the prevalence is increasing with increasing age and is more prevalent in the female gender; in addition, the overall mortality doubled in 2013 compared to 1994 (Thami Monfared, Byrnes, White & Zhang, 2022). In 2018, the revision of diagnostic criteria for AD in different stages defined the progression from Cognitive Unimpaired (CU) to MCI and finally to dementia (Jack et al., 2018). To be diagnosed, AD requires the presence of amyloid biomarkers in the cerebrospinal fluid (CSF), the presence of brain atrophy, and a clinical assessment that includes a rigorous history with neuropsychological testing to test global cognitive function (Jack et al., 2018; Kasper, Bancher, Eckert, Forstl, Frolich, Hort et al., 2020). In 2024, Frisoni et al. propose new European guidelines for the diagnosis of Alzheimer's disease, focusing on the importance of a subjective assessment of the patient, mainly regarding the profile of manifested symptoms, classifying the patient on the basis of 11 combinations of clinical manifestations, and finally testing for

appropriate biomarkers. The earliest evidence of Alzheimer's disease dates back to the studies of Alois Alzheimer (1906), in which the accumulation of Aβ-amyloid and the formation of neurofibrillary tangles of tau protein were observed post mortem. Brain imaging techniques have confirmed the presence and accumulation of plaques of Aβ-amyloid on the outside of the nerve cell and the presence of neurofibrillary tangles of tau protein on the inside; the plaques and tangles damage neurons and synaptic connectivity, initiating and contributing to the neurodegenerative process (Jack et al., 2018; Paroni, Bisceglia & Seripa, 2019). Studies in the scientific literature have also shown that the process of plaque accumulation, and thus tau protein, begins at least twenty years before the onset of clinical symptoms (Hanseeuw, Betensky, Jacobs, Schultz, Sepulcre, Becker et al., 2019; Breijyeh & Karaman, 2020). Other evidence relates to inflammatory processes and atrophy in specific brain areas. The inflammatory hypothesis is linked to the presence of Aβ amyloid and tau protein, which would trigger a response from the immune system and glial cells. The inflammatory process occurs when microglia fail to engulf all the waste material produced by Aβ-amyloid and tau protein tangles (Tai, Ghura, Koster, Liakaite, Maienschein, Kanabar et al., 2015; Gonzalez, Abud, Poon & Gylys, 2017). Cerebral atrophy, on the other hand, refers to the progressive loss of neurons either homogeneously and symmetrically, i.e., distributed throughout the brain, or asymmetrically, i.e. affecting only one part to a greater extent (Zhang, Lin & Wu, 2021). Genetically, however, the presence of the apoliprotein APOE in the e4 allelic form represents a strong risk for the

development of Alzheimer's disease (Spinney, 2014; Bertram & Tanzi, 2019). The person inherits one of three forms of the APOE gene, such as e2, e3 or e4. Having the e4 form increases the risk of developing Alzheimer's disease. One study found that of 1,770 diagnosed individuals from 26 Alzheimer's centers, 65% had at least one copy of the APOE e4 gene; however, the fact remains that inheriting this gene increases the risk of developing the disease (Karla wish et al, 2017). Down syndrome may also be a genetic risk factor, as chromosome 21 contains the gene that codes to produce amyloid precursor protein (APP). The presence of an extra copy of chromosome 21 may increase the production of Aβ amyloid fragments in the brain, increasing the likelihood of developing AD at an early age in this target population (Fortea, Vilaplana, Carmona-Iragui, Benejam, Videla, Barroeta et al., 2020; National Down Syndrome Society, 2021). Other genetic mutations have been considered by several studies, which suggest that abnormal changes in the sequence of the gene pair presenilin 1 and presenilin 2, which regulate the functions of the enzyme γ-secretase, one of the enzymes responsible for the degradation of the amyloid precursor protein (APP), predispose to the development of symptoms before the age of 65, sometimes at a young age (Cacace, Sleegers & Van Broeckhoven, 2016; Bertram & Tanzi, 2019). The National Institute on Aging and Alzheimer's Association (NIA-AA, 2011) has proposed a classification of AD into preclinical, AD-MCI and AD-dementia stages (Jack, Albert, Knopman, McKhann, Sperling, Carrillo et al., 2011).

In 2016, Dubois et al. defined two preclinical stages, the first of which is referred to as pre-symptomatic risk and the second as asymptomatic risk. The first is characterised by the possibility that the individual may develop AD due to genetic mutations, while the second requires the absence of clinical signs and symptoms but the presence of at least one biomarker for AD.

The National Institute on Aging / Alzheimer's Association (NIA / AA) (2011) proposed two subgroups:

A. stage 1, showing in vivo evidence of amyloid deposits in the brain from PET
B. stage 2, which shows in vivo evidence of amyloid deposits and neurodegeneration.

The quickest and least invasive way to diagnose preclinical AD is still unclear, especially in patients with no clinical signs and normal neuropsychological test scores.

Early symptoms include difficulty remembering conversations, names or recent events, loss of interest in daily or leisure activities, apathy, depression, and social withdrawal. Later symptoms include spatial and temporal disorientation, confusion, poor judgement, behavioral changes, and difficulties with thinking and reasoning. Memory and learning deficits affect memory for recent events, i.e., episodic memory, while implicit memory is preserved.

As the disease progresses, there are deficits in executive function with impaired critical thinking and judgement, ideational apraxia, and constructive apraxia.

The clinical framework also includes agnosia, a deficit in the perceptual analysis of the stimulus, which does not allow the individual to distinguish it from other objects.

Cognitive deficits also affect language, and in particular individuals with anomia, verbal paraphasia, diysnomia, characterised by difficulty in finding a word in spontaneous speech or writing, and impaired sentence repetition with reduced verbal fluency (Kempler & Goral, 2008; Possin, 2010; Làdavas, 2012; Ambron & Della Sala, 2017; Atri, 2019; Arvanitakis & Bennett, 2019, Zappalà, 2019; Alzheimer's Association, 2022).

The cognitive framework is often accompanied by behavioural-psychological symptoms (BPSD) that are difficult to treat. These include the presence of depressive symptoms, apathy, decreased motivation, emotional flattening, sudden mood changes, psychomotor agitation, irritability, physical and/or verbal aggression. In more advanced stages, psychotic symptoms may appear, with visual hallucinations and the phenomenon of wandering being predominant (Lyketsos, Carrillo, Ryan, Khachaturian, Trzepacz et al., 2011; Lanctot, Amatniek, Ancoli-Israel, Arnold, Ballard, Cohen-Mansfield et al., 2017; Nobis & Husain, 2018). Death is expected around 10 years after diagnosis and is often due to respiratory or cardiovascular disease.

Vascular disease (VD): is the most common form of dementia after Alzheimer's disease, with an estimated prevalence of 15-20% in Europe (Lobo et al.2000). Comorbid conditions include transient ischemic attacks,

hypertension, diabetes, dyslipidaemia, obesity, thyroid dysfunction, depressive symptoms, hearing loss, cancer, and other congenital disorders (for a comprehensive review see Morgan & Mc Auley, 2024). In terms of diagnostic criteria, neurological signs confirming cerebrovascular pathology should be present; for this reason, vascular disease can be considered "acquired", as suggested by Jiménez-Huete (2019).

The review by Bir et al. (2021) summarizes the factors supporting the diagnosis of VD, including the presence of a stroke, cerebral stroke, 3 to 6 months after symptomatic onset, risk factors, residual manifestations, family history of stroke, all supported by neuroimaging. In general, medium, and large infarct lesions in brain tissue and greatly reduced hippocampal volume are observed in these patients compared to patients with stroke but without vascular dementia (Zhou et al., 2023). However, cognitive decline due to vascular disease occurs not only in stroke patients but also in those with small vessel disease of the brain (Markus & de Leeuw, 2023). The severity of symptoms is typically oscillatory and fluctuating, with periods of stability followed by periods of deterioration in overall cognitive function, probably due to the nature and cerebral location of the vascular lesions (Bir et al., 2021). Cognitive symptoms include impairments in attention and concentration, processing speed and executive function, with difficulties in organizing thinking and decision making (Iadecola, 2013; O'Brien & Thomas, 2015; Dichgans & Leys,

2017;Wolters & Ikman, 2019). Neuropsychiatric symptoms are present, mainly apathy (Santos et al.2018).

Lewy Body Dementia (DLB):

Lewy body dementia (DLB): belongs to the synucleinopathies and is characterised by the accumulation of the protein alpha-synuclein in neuronal cells; this accumulation distinguishes it from Alzheimer's disease. Parkinson's disease also belongs to this group. In Europe, the prevalence is 10-15% (Alzheimer's Association, 2022).

DLB is diagnosed when motor symptoms are preceded by cognitive decline or when cognitive impairment begins before 1 year after the onset of motor symptoms (Prasad et al., 2023).

The typical diagnostic features are the onset of motor symptoms such as atypical parkinsonism, i.e., typical signs of PD such as gait disturbance, tremor and muscle rigidity, but without PD; the primary motor symptomatology is followed by memory deficits. In this form of dementia, attention and concentration problems are common, as are visuospatial deficits, visual hallucinations, decline in executive function with loss of problem-solving and decision-making skills, and depressive symptoms (Auning et al., 2011). Other symptoms include REM sleep disturbance, sleeplessness and waking with confusion (Gomperts, 2016; Armstrong, 2019).

Frontotemporal degeneration (FTD): is a dementia that falls under what is called tau-pathy, due to the increase of tau protein filaments in neuronal cells. Unlike the others, the first symptoms are related to behaviour and/or language. The atrophy is typically located in the temporal, frontal and insular areas (Mackenzie et al., 2010). of dementia We distinguish two variants (fronto-temporal Devenney, Ahmed & Hodges, 2019):

- **behavioural variant**, in which the following symptoms may appear at onset: behavioural disinhibition, apathy, loss of empathy, perseveration, obsessions and compulsivity, sexual disinhibition and hyperorality, impaired judgement. The decline begins with behavioural disturbances that also affect social cognition, progressing towards impairment of the cognitive sphere.
- **The language variant**, known as **primary progressive aphasia (PPA)** (Mesulam, 2001; Gorno-Tempini, Hillis, Weintraub, Kertesz, Mendez, Cappa, et al., 2011) is characterised by a speech disorder of neurodegenerative aetiology, which characterises its onset and remains predominant for much of the disease course. Onset usually occurs before the age of 65. It is divided into:

1. PPA with agrammatism: sentence structure is impoverished and naming is impaired;
2. Logopenic PPA: semantic and phonemic paraphasias are present. Sentence repetition is impaired and is also a common form in Alzheimer's disease.
3. Semantic PPA: characterised by impaired word comprehension. Naming is impaired, speech is vague, syntactic rules are impaired with the presence of

semantic paraphases and circumlocutions. Brain atrophy typically affects the left hemisphere.

Early- onset dementia: This rare form of dementia, which accounts for about 3 % of cases, can be caused by AD, VD, DLB or FTD. The main feature is the symptomatic onset, which is characteristic of dementia forms, in people younger than 65 years of age (Alzheimer's Association, 2022). The difficulty of diagnosis in these cases must be supported by good early diagnosis through clinical assessment of the patient using neuroimaging techniques, cognitive assessment, and family history (for a comprehensive review see Loi et al., 2023).

Mixed dementia: Many people with dementia have brain changes associated with more than one cause of dementia. This is known as mixed dementia. Some studies report that most people with Alzheimer's brain changes also present at autopsy have brain changes typical of a vascular disease (Fierini, 2020). Mixed dementia is particularly common in people aged 85 or older (Alzheimer's Association, 2022).

1.4 Modifiable risk factors

Modifiable risk factors are those that do not predict the certain and absolute onset of dementia. The studies in the literature that examine them provide important suggestions for the population, as their knowledge makes it possible to intervene in lifestyles not only in old age, but also in the earlier decades of life.

The Lancet Commission on the Prevention, Intervention and Treatment of Dementia (2024) identifies fourteen risk factors that contribute to the development of dementia and suggests ensuring good quality education, making hearing aids available to the population, treating depression effectively, promoting appropriate standards to prevent head injury, promoting physical activity, reducing cigarette smoking and alcohol consumption, preventing and reducing hypertension, dyslipidemia and diabetes, maintaining a healthy body weight, reducing exposure to environmental pollution and social isolation, and promoting screening for global cognitive function.

To date, the only viable prevention is lifestyle modification, intervening in the cognitive, psychological, physical and social domains.

The risk factors for the development of dementia that have been studied are analysed below. Some of these are common to the different etiological subtypes, while others relate to the onset of specific forms. Although age, genetics, female gender, and family history are not modifiable, other risk factors may be modifiable to reduce the risk of dementia. Examples of

modifiable risk factors include smoking, education, social and mental activity, prevention of vascular factors and diet. Addressing modifiable risk factors could prevent up to 40% of dementia cases (Livingston, Huntley, Sommerlad, Ames, Ballard, Banerjee et al, 2020).

- **Education and the construction of cognitive reserve** play a key role in that more years of education help to build a more resilient neural network. The number of years of formal education is not the only determinant of cognitive reserve (Urbanowitsch, et al., 2015). Having an intellectually stimulating job and engaging in other cognitive activities contribute to its construction (Stern, 2012). This is reminiscent of the concept of "*life-long-learning*", i.e., all that is learned during life experience. Fewer years of education and learning result in a weak cognitive reserve, less able to cope with the physiological changes of ageing but also with the neurodegenerative processes. Indeed, cognitive reserve per se would not protect against the appearance of neurodegenerative signs but it would protect against their negative effects by providing neuronal compensation mechanisms (Alvares Pereira et al., 2022).

- **Vascular factors**: these are present in comorbidity in the majority of dementia cases and include hypertension, diabetes, dyslipidemia, and high homocysteine levels (de Brujin et al., 2014). **Hypertension** is responsible for the thickening of blood vessels and thus a reduction in the amount of cerebral blood flow, while hypotension is responsible for ischemic events that can cause an

accumulation of Aβ-amyloid. **Dyslipidemia,** or change in cholesterol levels, share the APOE-e4 gene as a risk factor and cholesterol changes also affect synaptic connectivity; insulin deficiency or resistance is the causes of **type I and type II diabetes.** The association, still unclear, concerns the enzymes responsible for insulin degradation and the accumulation of Aβ-amyloid and tau protein phosphorylation. On the other hand, changes in **homocysteine** are correlated with vitamin B12 levels, cardiovascular disease and increased neurofibrillary tangles of tau protein (Santos, Snyder, Wu, Zhang, Echevarria & Alber, 2017).

- **Traumatic Brain Injury (TBI):** on certain parameters, such as the duration of loss of consciousness and post-traumatic amnesia, it is possible to classify the severity of TBI; moderate and severe levels represent potential risk factors for neurodegenerative processes, especially AD, FTD and Parkinson's disease (LoBue, et al., 2019). Moreover, this association is due to the cerebral mechanisms observed in the acute phase after trauma, which trigger an inflammatory response of the organism that is not sufficiently able to repair the injuries suffered (Kempuraj et al., 2020). Indeed, an accumulation of amyloid and tau protein, and the release of pro-inflammatory cytokines, have been demonstrated in the brain after TBI up to 7 days after the acute event (Brett et al., 2022).
- **Sleep disturbances**: these are a typical symptom of patients with AD and DLB patients and have also been hypothesised as predictors of onset (Hudon et al.,2020). Circadian rhythms play a pivotal role in maintaining health, and their

disruption has been linked to neurodegeneration, which in turn triggers Aβ-amyloid accumulation, tau protein accumulation and neuroinflammation processes, caused by oxidative stress and alteration of circulating melatonin (Leng et al., 2019; Wu et al., 2019).

- **General anesthetics**: the field of research concerning general anesthetics continues to generate controversial results. The hypothesis suggests that individuals undergoing general anaesthesia and its neurotoxic and neuroinflammatory effects may experience and elevated risk of cognitive decline associated with the processes of Aβ-amyloid accumulation, tau protein accumulation and other cellular modifications (Seitz, Reimer & Siddiquì, 2013; Hussain, Berger, Eckenhoff & Seitz, 2014; Belrose & Noppens, 2019).
- **Thyroid dysfunction** has been identified as both risk factor and a prodromal symptom and occurs during the normal ageing cycle. It has been associated with a progression of cognitive decline and appears to be implicated in the regulation of Aβ-amyloid (Latasa, Belandia & Pascual, 1998; Van Osch, Hogervorst, Combrinck & Smith, 2004; Gan & Pearce, 2012; Nomoto, Kinno, Ochiai, Kubota, Mori, Futamura et al., 2019).

- **Hypoacusis or hearing loss** has been determined as a risk factor for the development of dementia. It is included among the twelve risk factors according to the Lancet Commission on the Prevention, Intervention and Treatment of Dementia (Livingston et al., 2020; Livingston et al., 2024). Theories associating hearing loss with cognitive impairment primarily focus on

the role of neural networks involved in understanding spoken language and the intensity of cognitive effort required to recall and process phonological information already present in long-term memory (Livingston et al., 2020). Furthermore, this condition complicates the diagnosis of dementia or MCI, as few instruments are available to assess cognitive functioning in this population. As a result, misdiagnosis of cognitive impairment may occur (Riggio & Gangemi, 2025). The use of hearing aids is recommended not only to address hearing loss from a physiological perspective, but also for the social isolation that it can cause.

- **Environmental pollution:** the impact of environmental pollution on brain health is a subject of considerable interest in the scientific community. Studies have shown that long-term exposure to pollutants is likely to be detrimental to cognitive functions, owing to the accumulation of neurotoxic substances (Killian & Kitazawa, 2018). Further Epidemiological studies describe an association between reduced cognitive abilities and exposure to pollutants (Weuve, et al. 2021).
- **Depression** is a prodromal symptom of AD, and its role as a risk factor has also been a subject of study (Bennett & Thomas, 2014). During a major depressive episode or chronic depression (dysthymia), which remains untreated, there is impairment to cognitive functions (ex “pseudodementia”); however, the condition is reversible in certain cases (Gutzmann & Qazi, 2015). Furthermore, in cases where the episode occurs in old age, there is an increased risk for the individual as the depressive event presents neurobiological changes

(dysregulation of the hypothalamic-pituitary-adrenal axis, changes in serotonergic circuitry) that can be associated with the onset of Mild Cognitive Impairment, Alzheimer's Disease and other types of dementia, such as Vascular Disease (Sierksma, et al. 2010; Herbert & Lucassen, 2016; Ismail,2017; Steck, 2018).

- **Lifestyle**: It is important to note that, yet there is no evidence to suggest that lifestyle modifications can prevent neurodegenerative processes. However, it is understood that an individual's lifestyle can influence the onset of cognitive impairment by acting on epigenetic mechanisms and modifiable risk factors (Yu et al., 2020). For instance, the regular engagement in physical activity, the cessation of smoking, the management of obesity through dietary interventions, and the control of cardiovascular risk factors have been shown to reduce the likelihood of disease onset (Johnson et al., 2021).Additionally, the continuous stimulation and training of the brain through activities such as learning, engaging in new pastimes, and avoiding the loss of neurons and synaptic connectivity has been identified as a crucial factor in preventing neuronal loss and maintaining cognitive function (Trevisan et al., 2019).

- **Tobacco:** Tobacco smoking has been identified as a potential risk factor for the onset of dementia (Johnson et al., 2021). A comprehensive review of existing studies has revealed a heightened risk of dementia in smokers when compared

to ex-smokers or individuals who have been passively exposed to cigarette smoke. The Lancet Commission on the Prevention, Intervention and Treatment of Dementia (Livingston et al., 2024) has also confirmed smoking as a risk factor for dementia in longitudinal studies, particularly among smokers aged 33-44 years.

- **Alcohol consumption** has been identified as a potential risk factor, particularly in cases of juvenile onset. However, the evidence supporting a causal relationship between alcohol consumption and dementia remains inconclusive. Nonetheless, it is widely acknowledged that reducing alcohol intake can contribute to a decreased risk of developing the disease (Andrews et al., 2020).

- **Chronic stress** has been demonstrated to correlate with elevated glucocorticoid levels, dysfunction of the hypothalamic-pituitary-adrenal axis, and pro-inflammatory microglia responses, which have been shown to correlate with neuroinflammation and structural and functional changes in the frontal cortex and hippocampus (Sotiropoulos & Sousa, 2016; Bisht, Sharma, & Tremblay, 2018). Furthermore, a positive correlation has been demonstrated between glucocorticoids and Tau protein phosphorylation (Andrews et al., 2020). Furthermore, stress has been identified as a risk factor for additional diseases, e.g., cardiovascular disorders, which in turn, contribute to the onset of

neurodegenerative diseases (Bisht, Sharma, & Tremblay, 2018; Sotiropoulos & Sousa, 2016). A recent study (Christensen et al., 2023) investigated the association between perceived stress during the fourth and fifth decades of life and cognitive abilities. The results identified perceived stress as a predictor of less efficient cognitive abilities, especially in the verbal index and performance on the Wechsler's scale.

SECTION 2

The importance of early diagnosis and neuropsychological assessment of neurodegenerative diseases

In the preceding chapter, epidemiological data was described (World Report on Ageing and Health, 2015; Nichols, Steinmetz, Vollset, Fukutaki, Chalèk, Abd-Allah, et al., 2022), suggest a rapid growth of dementia cases, so much so that it is called a “global emergency”, affecting not only those going through the ageing phase, but also those approaching it, e.g. early dementia cases or those at risk (Alzheimer's Association, 2022).

The utilization of brain imaging tools and standardized cognitive assessments affords clinicians enhanced precision in determining the probability of diagnosis and identifying individuals at risk, who may not yet manifest the severity of cognitive symptoms on brain imaging. A significant challenge pertains to the timeliness of diagnosis, as patients and relatives often present to diagnostic and treatment services only when their daily lives are already significantly impaired by moderate to severe clinical symptoms. Moreover, patients frequently decline screening due to a reluctance to acknowledge even minor alterations in their cognitive function (Piras et al., 2016). It is often the individuals with the closest relationship to the patient, such as spouses or

children, who advocate for a neuropsychological assessment (Sommerlad et al., 2018).

2.1 Screening and early diagnosis of cognitive decline

The term "screening" is defined as a protocol or procedure that serves to detect the initial signs and symptoms of a specific disorder in an individual or a population (APA Dictionary). Screening programmers are frequently offered to individuals who, due to predetermined criteria, including hereditary criteria, are considered to be most at risk of developing that specific disorder.

Within the domain of neuropsychological assessment, screening tools must facilitate the discernment between normal and pathological conditions, thereby contributing to the formulation of a probable diagnostic hypothesis and potential preventive or curative treatments for the individual. The primary function of screening is to guide clinicians, when deemed appropriate, towards a more precise and comprehensive multidisciplinary diagnostic procedure. This procedure is characterised by the involvement of multiple professionals, including neurologists, geriatricians, psychologists, and other health professionals. The purpose of this collaborative approach is twofold: firstly, to identify biomarkers and risk factors, and secondly, to assess cognitive functions and the efficacy of treatments (Ganguli, 1997). The screening of cognitive functions thus represents one of the effective tools that enables the identification of “positive” subjects, who have obtained scores below the reference threshold of the normative sample or scores that are considered

borderline on the borderline between a situation of normality and pathology. However, screening would also be used to identify at-risk or sporadic cases, even if, at the time of assessment, these have scores that are considered to be within the normal range. Historically, screening was considered necessary only for individuals over 75 years of age or with a sustained risk, as therapeutic and preventive treatments were almost non-existent (Ashford, Borson, O'Hara, Dash, Frank, Robert, Shankle et al., 2007). Recent advancements in scientific research have advocated for widespread screening, even within primary care settings, for both preventive and treatment purposes, despite the irreversibility of the condition (Borson, Frank, Bayley, Boustani, Dean, Lin et al., 2013). The early detection of cases of dementia may facilitate the evaluation of pharmacological and neuropsychological interventions, which act to "slow down" the neurodegenerative process (Cappa, Allegri Del Signore et al., 2020). The administration of some treatments at an early stage may be beneficial, as they can assist the patient in maintaining a good quality of life for as long as possible by attempting to "stabilize" cognitive functioning. Furthermore, clinical trials of pharmaceutical interventions are predominantly conducted on subjects in the early stages of dementia or MCI, underscoring the imperative for the identification of cognitive profiles associated with the etiological subtypes of dementia and MCI, in addition to the exploration of other clinical characteristics that may facilitate the diagnosis. At risk (Budd, Haeberlein, Aisen, Barkhof, Chalkias, Chen, Cohen et al., 2022; Rahman, Hossen, Chowdhury, Bari, Tamanna, Sultana et al., 2023).

In summary, early diagnosis would allow the patient to be managed at an early stage, even before the cognitive impairment becomes disabling. This would help the patient and family member to adapt to the diagnosis and future management of the best treatment modalities, allowing them to familiarize themselves with the condition and learn its most important aspects (Rasmussen & Langerman, 2019). Moreover, early diagnosis has the potential to reduce healthcare expenditures and limitations within the healthcare system (Porsteinsson et al., 2021).

2.1.1 Data on screening in Italy

In Italy, the primary method of dementia screening is through specialist medical examinations and neuropsychological tests. However, a lack of a national dementia screening system exists, with access to diagnosis and treatment services being determined by the various Italian regions and provinces.

A study published in 2012 revealed that 62% of Italian municipalities had no dementia screening programmers, while only 3% had programmers that were universal in nature. However, 35% of municipalities had targeted screening programmers for population groups at risk, such as the elderly.

A subsequent study, conducted in 2017 by the Italian Ministry of Health, revealed that only 25.5% of individuals diagnosed with dementia in Italy received a correct diagnosis, while the remaining 74.5% remained undiagnosed

or untreated. Furthermore, only 14.2% of diagnosed patients had access to dementia-specific treatments.

The World Health Organization (2017) published a report highlighting the need to improve the diagnosis and treatment of dementia through the implementation of screening programmers, training of healthcare professionals, and access to diagnosis and treatment services for all patients.

2.3 Neuropsychological assessment in the evaluation of cognitive decline

Dementia screening includes measures involving the investigation of cognitive functioning, any symptoms that may be present, as well as an evaluation of the patient's autonomy.

First of all, it is essential to acknowledge the impact of anamnestic knowledge on the cognitive assessment of a subject. This knowledge refers to any pathologies that the subject may have experienced, as well as the symptomatology reported during the interview. The neuropsychological assessment should be conducted in a series of sequences, with the primary objectives including prognostic, diagnostic, follow-up and intervention planning purposes. As suggested by Di Nuovo and Vianello (2013), the phases of neuropsychological assessment are divided into *anamnestic collection, clinical interview and neuropsychological assessment.*[5]

[5] For a more in-depth examination of the domain of neuropsychological assessment in adults recommend reading Mondini, S., Cappelletti, M. & Arcara, G. (2022). Methodology in Neuropsychological Assessment: An interpretative approach to guide clinical practice. Routledge: London.

The anamnestic collection process entails the processing and observation of data deemed significant provided by the patient or a family member. In detail the presence of risk factors, any previous pathologies, the subject's psychological history and the presence of symptoms present at the time of the interview, both cognitive and behavioral are investigated. At this stage it is imperative to examine the severity of the symptomatology. and how it is disabling is for the subject's autonomy. The collection of data in intended to provide the clinician with an initial clinical representation that, if interpreted correctly, will inform the subsequent instrumental examinations and the scores obtained on cognitive tests.

The clinician must consider the symptoms described by the subject or the family member, as well as the observations and interview results. Conducting a clinical interview with the patient, in fact, provides information regarding cognitive functioning, relating for example to the quality of speech, thought disorders if present, dysarthria, apraxia, motor symptoms, facies and mimicry. In addition, the psychological sphere, and related emotions, such as anxiety, phobias, and obsessions, are explored during the interview. Mood, awareness of pathology, and ideo-motor slowing down.

Neuropsychological assessment is a process that involves the administration of standardized tests for the purpose of evaluating and quantifying cognitive abilities and residual personality traits, in addition to behavior, with the objective of identifying areas in which intervention is required. The cognitive domains that are assessed include learning and memory, visuospatial and

perceptual functions, attention, language, executive functions, and psychomotor skills. Preference is usually given to screening measures for global, standardized tests that investigate the different domains of cognitive functioning. The selection of the tests to be used depends on several variables, including the impaired cognitive functions reported by the patient and family members, the information gathered in the history and the clinical interview. Additionally, the selection is informed by the subject's age and educational background. Subsequent to this evaluation, a detailed appraisal of specific cognitive domains is warranted. However, due to temporal constraints, the administration of a unidimensional test of global cognitive functioning is frequently prioritized. This is followed by a meticulous evaluation of specific cognitive functions, if deemed essential by the clinician.

The utilization of outpatient settings is of paramount importance due to temporal constraints and, in certain instances, a paucity of professionals with the requisite expertise in this domain (Alzheimer's Association, 2022). There is, therefore, an imperative for the development of standardized screening tests that are both straightforward to administer and interpret, and that are suitable for populations with limited education and diverse ethnicities (Franzen et al., 2020).

2.4 Psychometric screening tools for global cognitive functioning: MMSE, MoCA & ACE-III

In the years that followed, there have been several attempts to standardize the instruments to be used in neuropsychological assessment. The Consortium to Establish a Registry for Alzheimer's Disease (Morris et al., 1989) proposed a battery of neuropsychological tests designed to measure verbal fluency, naming, constructive praxis and memory. Notably, the battery encompasses the Boston Naming Test, which quantifies categorical fluency and the recall of constructive praxis for figure construction, memorization, recall, and word list recognition. Additionally, it incorporates the Mini-Mental State Examination. Conversely, a survey conducted in Europe (Maruta et al., 2011) of the 213 most frequently utilised tests, some of which are not validated across all countries, concluded that not all tests are suitable for clinical practice.

The heterogeneity of instruments, both in clinical practice and in research, and therefore the resulting fragmentation of data, the impossibility of comparing the results of studies, and the need for tests for global and specific cognitive functioning, are factors highlighted in another study conducted also in Europe (Costa et al., 2017). In Italy, a survey of 501 Diagnosis and Treatment Centers revealed the utilization of at least one test for episodic, verbal, and visual memory, attention, constructive praxis, verbal fluency and executive functions

as part of the diagnostic process (Di Pucchio et al., 2018). Conversely, certain instruments have been disused due to their inability to discern cognitive decline with adequate sensitivity, a prime example being the Wechsler Adult Intelligence Scale. The validation and applicability of cognitive screening instruments is contingent upon their possession of robust psychometric properties (Aiello, Rimoldi, Bolognini, Appollonio, & Arcara, 2022). However, certain psychometric tests often fail to meet these standards, which can have a detrimental impact on the results obtained, particularly in cases where individuals are borderline cognitively impaired but not demented (Pottie, Rahal, Jaramillo, Birtwhistle, Thombs, Singh et al., 2016). Pottie et al. emphasize the importance of adequate and individual screening, given the possibility of the available tests to incur the error of "false positives" or to fail to show any deterioration (see, for example, 1 in 8-10 people after administering the Mini-Mental State Examination (MMSE) and 1 in 4 people after the Montreal Cognitive Assessment (MoCA).

In this regard, overestimation or underestimation of the diagnosis may be influenced by certain variables, such as cross-cultural adaptations of cognitive screening tests (Uysal-Bozkir, Parlevliet, de Rooij, 2013), or sensory deficits, e.g. hearing loss or low vision. These two conditions frequently manifest during the ageing phase; however, the present data demonstrate a paucity of validations in populations affected by these deficits, thereby rendering the interpretation of the entire test and the resulting score ambiguous for clinicians, with some instances of overestimation of diagnosis (Völter, Götze, Dazert, Wir

th, & Thomas, 2020; Riggio & Gangemi, 2025). It is imperative that cognitive test validations are conducted with an adequate sample size, representative of the population (De Roeck, De Deyn, Dierckx, & Engelborghs, 2019). The selection of points for cut-off is to be approached with caution during the interpretation of results, with consideration given to the age and educational attainment of the sample, which have the capacity to influence the diagnostic estimate (Rosli, Tan, Gray, Subramanian, Chin, 2015). The MoCA-B, for instance, is a modified version of the MoCA, designed to be less dependent on literacy levels as the recruited sample has less than five years of schooling (Julayanont, Tangwongchai, Hemrungrojn, Tunvirachaisakul, Phanthumchinda, Hongsawat, 2015).

In addition, there are versions of the MoCA Blind/Hearing Impairment (Wittich et al., 2010; Dawes et al., 2023) that address sensory problems. Furthermore, a recent Italian study (Aiello, Rimoldi, Bolognini, Appollonio & Arcara, 2022) analysed some of the most commonly used cognitive tests for the assessment of both global cognitive functioning and specific cognitive functions. The conclusions of the authors concern the psychometric qualities and validations of the tests. The authors identify a need for cognitive tests to be subjected to factor analysis and for construct and criterion validity to be well distinguished from each other. Furthermore, the need was identified for developing instruments and new versions of existing instruments. These instruments should be applicable across diverse populations. However, it is imperative to acknowledge that, akin to any instrument, a test cannot be used as the sole

diagnostic tool. Instead, it must be interpreted in conjunction with other clinical information and complementary test results. In summary, neuropsychological assessment in adults and the elderly is crucial for both early and ongoing diagnosis, as well as for prevention in patients with possible brain signs. Consequently, it is instrumental in prognosis and treatment management (Cook et al., 2020).

2.4.1 MMSE, MoCA and ACE-III

The assessment of global cognitive functioning employs screening instruments (Claassen, 2005), such as the Mini-Mental State Examination (MMSE) (Folstein & Folstein, 1975) and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2003). In addition to the instruments mentioned, there are other psychometric tests that can discriminate between pathology and normality, such as the Addenbrooke's Cognitive Examination, in its most recent version, ACE-III (Hsieh et al., 2013; Noone, 2015; Hodges & Larner, 2017). The following descriptions outline the tools just mentioned.

MMSE is a widely utilised tool for its simplicity and brevity of administration. It is a highly versatile instrument, facilitating the comparison of scores in follow-ups and providing a substantial body of data in the literature from research (Strauss et al., 2012).

The test comprises items with verbal and performance tests that explore temporal (year, day of the week, month, date, season) and spatial orientation (city, region, province, place of administration, plane), immediate memory and deferred recall of three words (house, bread, cat attention and calculation (subtraction and spelling backwards of a word), language (naming two objects, comprehension of oral and written verbal language, writing, repetition of a sentence), and visuo-constructive praxis (copying two intersecting pentagons). The maximum score that can be attained is 30, and the required administration time is approximately 5-10 minutes. The test is favored for its simplicity and the swiftness of its administration; however, certain limitations have been identified in the literature, including the absence of specific tests to evaluate executive functioning (a feature present, for example, in the MoCA) and the test's low sensitivity in detecting mild cognitive impairment (Lonie et al., 2009; Velayudhan et al., 2014). Notwithstanding these limitations, the test remains the neuropsychological instrument of reference for the prescription of drug treatment in cases of dementia (Di Pucchio et al., 2018). Folstein et al. (2010) created a second version of the MMSE consisting of a short version, the standard version and an extended version. The short version is derived from the standard version and includes only the items related to language, attention and calculation and constructive practice. In contrast, the extended version incorporates two additional items, facilitating the assessment of narrative memory and processing speed (Folstein et al., 2010). Each version of the MMSE-2 is administered in two alternative forms, with different items, to avoid

the learning effect (Di Pucchio et al., 2018). To date, there is an absence of literature on the validation of the MMSE-2 in Italy. While there have been validations of the MMSE with varying results, the cut-offs identified in Italy differ from those reported elsewhere (Di Pucchio et al., 2018). Measso et al. (1993) identified a cut-off of 23.8 in a sample consisting of more than 900 subjects recruited from many Italian regions in the North, Centre and South, aged 79 years; the scores include a correction for age and schooling.

The validation of Magni et al. (1996) was conducted in three distinct Italian cities on a sample of 1,169 individuals aged 65 years and over. The established overcut-off is 22, and this validation also incorporates the correction of scores based on the subjects' socio-anagraphic data. Carpinelli Mazzi et al. (2020) identified a cut-off of 24.9 in a population of 314 subjects in Southern Italy, specifically in the Campania population.

Recently, a validation was carried out on the population of both Northern Italy and Italian Switzerland (Foderaro et al., 2022). The item “house, bread, cat” was changed to “house, FLOWER, cat” to reduce the common error of “dog”, probably due to both possible sensory deficits and ease of remembering the word dog (in italian language the sound of “bread”→**pane** is very similar to the word “dog”→ **cane**). 301 healthy subjects aged 20 to 95 years were recruited. The cut-off identified was 26.01. In all validations, the variables gender, age, and years of education were found to be single. Significant predictors. The MMSE in Italy has also been validated in telephone (form cut-off 18.49)

(Quaranta et al., 2024) and videoconferencing, through a pilot study (Carotenuto et al., 2018), for remote screening.

In general, for outpatient purposes, the scores obtained are divided into three severity ranges: scores above/equal to 24 define a condition as normal, scores between 20 and 24 define mild cognitive impairment, 20-10 define moderate impairment, and scores below 10 define severe impairment (Perneczky et al., 2006; Alzheimer's Association, 2022).

MoCA: is a standardized test designed primarily to identify individuals with mild cognitive impairment (Nasreddine et al., 2005). It consists of items assessing executive function, attention, and visuospatial ability (short form of the Trail Making Test - form b, clock drawing test, cube copying, abstractions, subtraction and letter series), language (sentence repetition and phonemic fluency), spatial and temporal orientation, immediate and delayed memory (learning and recalling five words) with recognition tests. The cut-off score is 26/30, with one point added for less than 12 years of schooling. The scores are then adjusted for education. In people with Alzheimer's disease, a score between 18 and 25 indicates mild decline, a score between 20 and 13 indicates moderate decline, and a score below 13 indicates severe decline (Nasreddine et al., 2005). The MoCA has been shown to be more sensitive than the MMSE in detecting MCI, but less specific than the latter (Luis et al. 2009).

Also for this test, there are several Italian validations, among which the one carried out by Pirrotta et al. (2014), through the analysis of the ROC curve,

identifies a cut-off equal to 15.5 on 287 recruited subjects. This is therefore a lower cut-off than the original version, probably depending on the socio-demographic characteristics of the sample, a value also confirmed by the validation conducted by Santangelo et al. (2014). Through a further validation carried out on 225 patients, Conti et al. (2015) identify two cut-offs: 17.36 and 19.26. Again, for Bosco et al. (2017), a cut-off of 14 discriminates likely AD subjects from controls, while a cut-off of 17 discriminates MCI from normal subjects. Finally, in the validation of Pirani et al. (2022), the best cut-off is <25, confirming an accurate test to discriminate the cognitive performance of subjects with MCI from those with dementia.

ACE-III: Validated by Hsieh et al. (2013) to detect cognitive decline and differentiate between AD and FTD (this test assesses spatial orientation (place where the test is administered, plane, city, region and state) and temporal orientation (date, day of week, month, year, season), short-term memory, learning and delayed recall (through two tests: memorizing and recalling 'house, bread, cat' and a first name, surname and address), episodic memory (memory item recognition regarding first name, surname and address), language (comprehension, word and sentence repetition, writing, naming and address), and address), episodic memory (recognition of memory items relating

to first name, surname and address), language (verbal comprehension, word and sentence repetition, writing, naming of 12 items, semantic understanding of naming, reading), visual-perceptual skills (copying of intersecting figures, copying of dice, clock, counting of dots and recognition of fragmented letters). It was recommended as a screening tool by the UK Alzheimer's Society in 2015 (Jubb et al., 2015) and takes approximately 20 minutes to administer. The study of psychometric the qualities of the ACE-III demonstrated high sensitivity and specificity[6] , with recommended of 88 (sensitivity =1.0; specificity =0.96) and 82 (sensitivity =0.93; specificity =1.0) cut-offs (Hodges & Lerner, 2017)

The Italian validation is by Pigliautile et al. (2019), and provides a maximum of 100. No was identified score cut-off but, by correcting the scores for age and schooling, the reference value is 72.03. Between 68.68 and 72.02, borderline scores are identified.

Although more time-consuming to administer than the MMSE and therefore more suited to specialist settings, the ACE-III has been shown to be easier to use, acceptable to patients, and useful for diagnostic purposes in identifying cognitive impairment in a variety of etiological subtypes of dementia and MCI (Bruno et al., 2019). There are several translations and validations of the test in the literature (see for example Matias-Guiu et al. 2016; Wang et al., 2017; Peixoto et al., 2018; Takenoshita et al., 2019; Kan et al., 2019; Bruno et al., 2020; Kaczmarek, et al.2022).

[6] **Sensitivity** indicates the ability of a test to correctly identify those who have a certain condition. **Specificity** measures the ability of a test to correctly identify those who do not have the condition. Both are essential for assessing the reliability of a diagnostic test. The values should be close to 1.

2.4.2 MMSE, MoCA and ACE-III: instruments compared

A number of studies have compared the psychometric properties of the MoCA, the ACE-III and the MMSE as assessment tools in patients with cognitive disorders. For example, the MoCA scored higher in terms of both sensitivity, i.e. in detecting middle-aged people with MCI, and specificity, i.e. the test's ability to detect truly healthy people, than the MMSE (Smith, Gildeh, & Holmes, 2007; Alagiakrishnan, Zhao, Mereu, Senior, & Senthilselvan, 2013; Sokolowska, Sokolowski, Polak-Szabela, Mazur, Podhorecka, & Kedziora-Kornatowska, 2018; De Roeck, De Deyn, Dierckx, & Engelborghs, 2019). This finding is supported by a meta-analysis that recommends against using the MMSE in cases of suspected MCI, as the psychometric specificity of the MoCA is statistically superior for mild cognitive impairment (Breton, Casey, & Arnaoutoglou, 2019). In light of these findings, it is possible to speculate that the underestimation of the diagnosis of mild cognitive decline may be partly due to the use of cognitive tests such as the MMSE, which are mainly administered for screening purposes in primary care. However, the MMSE continues to be used and recommended as a cognitive screening tool (Aiello et al., 2022).

With regard to the ACE-III, its psychometric properties are superior to those of the MoCA and the MMSE for the diagnosis of AD and FTD (Hodges & Larner, 2017). Furthermore, in a sample of 249 subjects, differences were found in the

areas under the ROC curve (AUC), making the use of the ACE-III preferable to the MoCA and MMSE in both MCI (0.891, 0.831, 0.782) and dementia (0.930, 0.854, 0.856) (Senda, Terada, Takenoshita, Hayashi, Yabe, Imai et al., 2020).

Another study conducted in the Chinese population (Wang, Zheng, Xu, Sun, Zhang, & Shi, 2019) suggested that both ACE-III and MoCA have acceptable sensitivity and specificity in differentiating subjects with MCI from controls. However, compared with ACE-III, MoCA may be more suitable for screening MCI, as it has a higher sensitivity for detecting mild cognitive decline.

Again, according to the results of one study, the ACE-III was shown to have the best diagnostic accuracy compared with the MMSE and the MoCA, allowing almost perfect discrimination between controls and patients with AD (Matías-Guiu, Valles-Salgado, Rognoni, Hamre-Gil, Moreno-Ramos, et al., 2017). In general, the ACE-III showed good discrimination between healthy subjects and patients with AD and FTD; it also showed good psychometric properties for the detection of mild cognitive impairment (Matías-Guiu, Cortés-Martínez, Valles-Salgado, Rognoni, Fernández-Matarrubia, Moreno-Ramos, & Matías-Guiu, 2017). It should be remembered that the ACE-III, like any test in the literature, is influenced by demographic and educational variables (Bruno & Vignaga, 2019).

Also for the ACE-III, as for the MoCA in the Italian version (Aiello, et al., 2022), a conversion of scores to MMSE scores is foreseen (Matias-Guiu et al., 2018), since the latter test is widely used, although it now has all the

characteristics to be replaced or used in a more limited way. The conversion of the scores is not present in the literature for the Italian version.

In the future, the study and comparison of cognitive tests and the updating of psychometric properties could be crucial for the advancement of research on the detection of MCI and other early conditions, contributing to the earliest possible diagnosis and treatment (Chun, Seward, Patterson, Melton et al., 2021).

2.5 Conclusion

In general, the main screening tools for global cognitive function are described in this chapter. As described, the following tests have been found useful in clinical practice to contribute to the diagnostic process in neurodegenerative diseases. Limitations that have been identified with the MMSE, for example, relate to the detection of MCI and the incomplete exploration of certain cognitive functions, such as executive function. The MoCA, on the other hand, seems to compensate well for these limitations and is mainly used to identify MCI.

The ACE-III, on the other hand, seems to be a good test, competitive with the above-mentioned tests, both for the diagnosis of dementia and MCI. However, it takes longer to administer, which makes it less suitable for use in outpatient settings, where both speed and accuracy are important. A short version of the

ACE-III could overcome the limitations of the MMSE and provide a single test with good psychometric properties for both MCI and dementia. This is the aim of the following work: to search for a short version that might be suitable for diagnosing both MCI and dementia.

The next chapter presents the empirical work to validate the M-ACE short version of Hsieh et al.2014 and to derive another version from the Mokken Scale Analysis.

SECTION 3

The Mini-Addenbrooke's Cognitive Examination (M-ACE): a new short-form *"M-ACE 6"* based on the Mokken Scale Analysis

The Mini-Addenbrooke's Cognitive Examination (M-ACE) is the short version of the ACE-III. It was constructed by Hsieh in 2015 and derived from the extended version using the non-parametric statistical technique of Mokken Scale Analysis (MSA). The M-ACE consists of five items that examine the domains of attention and orientation, memory, verbal fluency, and visuospatial ability. The items and their cognitive domains are summarised in **Table 1**.

Cognitive domain	**Items**
Time orientation and attention	Date, day of week, month, year
Memory	Learning, short-term Delayed recall of a first name, surname and address
Categorical fluency	List of items belonging to a category (e.g. animals)
Visual-spatial ability	Clock Drawing Test

Tab.1 Cognitive domains and items included in the M-ACE (Hsieh, 2015)

The extended version of the ACE-III includes the item "season", which refers to time orientation; the M-ACE excludes this item, as it is considered problematic for inhabitants of certain locations (e.g., the tropics). The total score is 30. In the original version, the cut-offs identified by the ROC curve are 21 and 25, with a model sensitivity of 0.61 and 0.85 and a specificity of 1.0 and 0.87, respectively. The scale was shown to have good internal consistency (Cronbach's = 0.833) (Hsieh et al., 2015).
In New Zealand, where the test has been validated, it is recommended for use as a useful, simple, and short-term screening test.

3.1 Validation and comparison studies of M-ACE with other screening instruments

There are studies in the literature on the normative data of the M-ACE that have demonstrated its psychometric properties (**Table 2**) by comparing it with the MMSE and versions of the ACE and, in some cases, with the MoCA. The subjects whose performance is assessed are generally healthy subjects with MCI and dementia (in most cases the largest number of subjects are included in the AD and FTD diagnostic groups). In the original version, subjects with PPA were also included. In Italy, only one study has investigated the diagnostic capacity of M-ACE in a group of subjects with HIV dementia (Trunfio et al., 2022); this etiological subtype is characterised by slowed thinking and expression, concentration difficulties and apathy (Heaton et al., 2011). Here is the comparison between M-ACE and the screening tool identified for these specific cases (International HIV Dementia Scale, Sacktor et al., 2005).

In general, studies in clinical populations have shown good psychometric qualities for the M-ACE, competing with, but often slightly inferior to, the ACE and the MoCA. Compared with the MMSE, the M-ACE showed higher sensitivity, specificity and accuracy, and better discrimination between healthy subjects and those with cognitive decline, even in long-term care settings

(Grasina et al.2024). However, a systematic review (Beishon et al., 2019) showed that the original version of the M-ACE has variable sensitivity and greater variability in specificity, depending on the cut-off established in the studies.

In addition, due to linguistic and cultural differences, some studies have modified versions of the M-ACE, either by not including all the items of the original version or by adding others with respect to the different domains. For example, in the Brazilian version by Okada-Olivera et al. (2024), the following items were identified by Mokken analysis: spatial orientation, anterograde memory, retrograde memory, delayed recall, verbal fluency, naming and semantic comprehension. In this version there are no items testing visuospatial abilities and categorical fluency has been replaced by verbal fluency. The items from the residual memory have been added to the retrograde memory, i.e., questions on semantic memory (who the President of the Republic is, who is the President of the United States, who is the former Pope, who is the President of the United States who was assassinated in the 1960s); spatial orientation replaces temporal orientation. Pan et al. (2021) instead identifies an M-ACE consisting of anterograde memory, recall, and also include the recognition item, in which the subject is given options to choose from that act as an aid to remembering the items studied in this domain. Categorical fluency remains and the 12-digit naming item is added. Again, there are no items testing visuospatial ability. In this regard, it should be clarified that the choice of items in the

original version was derived from both the MSA and the clinical choices of the authors, who preferred one item over the other (Hsieh, et al.2015).

Authors	**Sample**	**Cut-off**	**AUC**	**Sensitivity**	**Specifity**	**Accuracy**	**Cronbach 's Alpha**
Hsieh et al., 2015 (New Zealand)	23 subjects bvFTD, 82 PPA, 38 AD, 21 CBS, 78 non-clinical group	21 25		0.61 0.85	1.0 0.87		0.83
Matias-Guiu et al., 2016 (Spain)	92 controls, 46 AD, 4 VD, 9 MD, 11PD, 6 LBD, 5 FTD, 1 dementia, 1 atypical parkinsonism with dementia alkolic	16	0.94	86.7%	87%		0.828
Hsieh et al., 2016 (New Zealand)	45 non-clinical group, 27 pure ALS, 19 ALS plus, 24 ALSFTD	25		0.65	0.90		
Miranda, et al.2018 (Brazil)	23 subjects with AD 36 with MCI	20	0.805	95.65%	90.16%	91.67%	0.8
Larner, 2019 (England)	336 subjects with dementia and 419 with subjective memory impairment	25		0.967	0.458		
Yang et al. 2019 (China)	51 non-clinical group, 64 subjects with MCI, 54 subjects with moderate dementia	MCI=25/26 Moderate dementia=21/22	0.87	MCI=0.88 Moderate dementia=0.96	MCI=0.72 Moderate dementia=0.87	0.97	
Qassem, et al. 2020	37 subjects with dementia (AD, vascular dementia, LBD) and 43 non-clinical group	18		92%	95%	94%	
Senda et al., 2020	50 non-clinical group, 94 MCI, dementia 105	MCI=25/26 Dementia=18/19	MCI=0.85 Dementia=0.917	MCI=0.77 Dementia=0.80	MCI=0.72 Dementia=0.85		

Quassem et al., 2021	24 subjects with MCI and 52 non-clinical group			87.5%	84.6%	85.5%	
Peixoto, et al.2021 (Portugal)	130 healthy subjects						0.84
Pan et al., 2021 (China)	431 checks and 285 MCIs	25	0.892	83.03%	79.81%		0.77
Trunfio et al., 2022 (Italy)	231 subjects with HIV of whom 112 subjects with HIV-associated dementia	<25	0.97	89.3%	94.1%		
Kaczmarek, et al.2022 (Polish)	386 healthy subjects	20					
Grasina, et al. 2024 (Portugal)	190 LTCs, 71 non-clinical group, 125 with cognitive impairment but not dementia	17	0.81	81.7%	74.4%		0.85
Okada-Oliveira, et al.2024 (Brazil)	232 controls, 82 subjects with cognitive decline not due to dementia, 38 subjects with dementia	43/51	0.62	59%	80%		0.77
Pourshams et al., 2024 (Persian)	30 non-clinical group , 25 MCI, 32 subjects with dementia	MCI=27.5 Dementia=20.5	MCI=1 Dementia=0 .99				0.91
Salgado, et al.2024 (Spain)	84 non-clinical group and 56 MCIs	20	0.867	78.57%	80.95%		
McCarthy et al., 2024 (England)	79 subjects with cognitive decline	19 mild decline 13 moderate decline	0.81 0.18				

Tab.2 Psychometric characteristics of the M-ACE; AD=Alzheimer's disease; bvFTD=behavioral fronto-temporal dementia; PPA=progressive primary aphasia; CBS=cortico-basal dementia; VD= vascular dementia; MD=mixed dementia; PD=Parkinson's disease; LBD=Lewy Body Dementia; ALS=amyotrophic lateral sclerosis; MCI=mild cognitive impairment;

3.2 Aims

Currently, the psychometric properties of the M-ACE in healthy subjects and in subjects with dementia have not been studied in Italy, and there are no Italian comparisons between this test and the gold standards for cognitive decline.

The main objective of the following work is to obtain normative M-ACE data on an Italian sample of healthy and clinical subjects.

The desire to study the instrument stems from its psychometric goodness demonstrated in studies in the literature, its ability to discriminate between healthy subjects and those with cognitive decline, and its short administration time (approximately 5-10 minutes), which is useful in outpatient settings.

The Italian validation of the ACE-III (Pigliautile et al., 2019) suggests a short form of the instrument based on the cut-offs identified by Hsieh et al. (2015).

The present study aims to provide empirical evidence in support of a short form standardized for the Italian population, also through the application of Mokken Scale Analysis, assuming a version that also differs in the choice of items for our sample.

Finally, a comparison between M-ACE, ACE-III, MMSE and the derived version is proposed.

3.3 Methods and materials

Sample

Participants were recruited at the Department of Neurology, Policlinico Universitario "G.Martino", Messina, using the convenience sampling method. The sample was divided into a control group, composed of healthy subjects, and a clinical group composed of subjects with cognitive decline. The inclusion criteria according to which participants were selected for the control group were age over 50 years, absence of psychiatric/neurological disorder; participants in the clinical group were selected on the basis of diagnostic criteria for MCI and dementia (Jack, et al. 2018), including scores of 24 and below on the MMSE, brain imaging (MRI) in which the presence of brain atrophy was detected. For MCI subjects, scores from 24 to 21 were considered. Recruitment took place from January 2023 to June 2024 under the supervision of a neurology specialist from the department. The sample consisted of 181 subjects, 105 women and 76 men, with a mean age of M=75.1, SD=8.13 for women and M=75.7, SD=7. 97 for men. The clinical group was composed by 110 subjects with cognitive decline; the non-clinical group consisted of 71 participants. Of the group with cognitive decline, 37 are subjects diagnosed with MCI and 73 are diagnosed with dementia. (**Table 3**). For the comparison of psychometric measurements in subjects with and without cognitive decline, two subgroups were created in

which the conditions of dementia and MCI were taken into comparison with the entire sample.

The two subgroups below:

- "Dementia" vs. "No dementia", in which "no dementia" consists of MCI and healthy subjects;
- "MCI vs. dementia";

		SUBGROUPS OF COGNITIVE DECLINE		
	Controls	**Cognitive Decline**	**MCI**	**Dementia**
N	71	110	37	73
AGE	M=73.6, DS=8.41	M=76.6, DS=7.57	M=75.7, DS=7.95	M=76.9, DS=7.71
EDUCATION	M=11.61, DS=4.38	M=8.14, DS=4.15	M=8.97, DS=4.62	M=7.85, DS=4.03
ACE-III	M=77.9, DS=10.03	M=48.1, DS=14.93	M=61.2, DS=7.00	M=42.8, DS=13.15
MMSE	M=27.2, DS=1.58	M=18.7, DS=4.47	M=22.6, DS=1.20	M=17.2, DS=4.33

Tab.3- Characteristics of sample

All subjects were informed of the purpose of the study and were given a paper copy of the informed consent form to read and sign if they agreed. All 181

subjects consented. In cases where the administrator had doubts that subjects in the clinical group did not understand the rationale of the present study, the consent form was signed by the accompanying person present. The study was approved by the Ethics Committee of the Department of Cognitive, Psychological, Educational and Cultural Studies (COSPECS) of the University of Messina.

Tools and Procedures

In the evaluation, the sample was subjected to the following instruments presented below in order of administration:

- Addenbrooke's Cognitive Examination- III **(ACE-III)** (Pigliautile et al., 2019). The test consists of 23 items which are designed to measure the following cognitive domains: attention and orientation, memory, language, fluency and visuo-perceptual skills. The maximum score is 100. The scale can be divided into sub-scores:
    - Attention and orientation: 0-18;
    - Memory: 0-18;
    - Fluency: 0-7;
    - Language: 0-26;
    - Visual perception skills: 0-16;
- The scale developed by Pigliautile et al. (2019) for Italy does not establish a cut-off score; instead, it corrects for age and education; the authors proposed

inner and outer tolerance limits for the total and subscale in order to discriminate between healthy and pathological subjects (not normal: total score ≤68.68; borderline (68.69 < total score < 72.03), totally normal (≥ 72.03). The time taken to administer the test was approximately 20-30 minutes;

- Geriatric Depression Scale (**GDS**) (Yesavage et al., 1982) to investigate the presence of depressive symptoms. It consists of 30 dichotomous items to which the subject must answer with "Yes" or "No". Due to the nature of the items, the GDS was used as interference between the administration of the two cognitive tests, so as not to cognitively fatigue the subject. The time taken to administer the test was approximately 8-10 minutes;

- Mini- Mental State Examination (**MMSE**) (Measso, et al.1993); The measure consists of 11 questions covering various cognitive domains, including: Temporal and spatial orientation (date, place, season), Short-term memory (remembering words or numbers), Attention and calculation (basic mathematical operations), Remembering words (long-term memory), Language (verbal comprehension and production), Visuospatial abilities (copying a geometric figure). The maximum score that can be attained is 30, with lower scores indicating a possible impairment of cognitive functions. A score below 24 may suggest the presence of dementia or other forms of cognitive deterioration; however, the interpretation also depends on age, level

of education and clinical context. The items were not administered equal present in the ACE-III in order to avoid the learning effect; (temporal and spatial orientation, three-item register and recall, subtraction).

The tests administered were without the presence third parties or of family members, who were consulted afterwards, when a clinical and anamnestic interview took place. This followed was at a later date by a discussion with the referring neurologist and an interview to return the results with the subject and family members.

Data Analysis

Data analyses were performed using Jamovi and R (The Jamovi Project, 2024; R core team, 2024). The R packages used were: mokken (Van der Ark, 2007), lavaan (Yvees, 2012), pROC (Robin et al.2011).

Descriptive analyses were used to explore the sample. Skewness, kurtosis and the Shapiro-Wilk test were used to check the distribution of the data. Levene's test for homogeneity of variances between groups was performed with reference to the test scores used. Before standardization, a correlation matrix between the ACE-III items was carried out to determine the relationship between the variables.

For the standardization of the M-ACE, the pROC package was used to obtain the ROC curve, the area under the curve (AUC), the best cut-off and indices of sensitivity and specificity. Logistic regression and classification tables were used to assess predictive validity.

To explore which items of the ACE-III were most discriminative, Mokken Scale Analysis (MSA), a non-parametric technique for automated item selection, was applied following the original study by Hsieh et al. (2015). The result is a set of scaled ordinal items (Mokken, 1971; Wind et al., 2017). With this method, some items are not selected because they do not meet the goodness of fit of the model.

In order to study the item hierarchy and investigate the item difficulty, Hsieh et al. (2015) applied the MSA to the ACE-III to derive the M-ACE. The MSA aims to derive the one-dimensionality of ordinal items by examining the latent construct, which in this case is considered to be global cognitive functioning. The coefficients to be considered during an MSA are described as follows:[7]

1. ***"Scalability*** H coefficient the entire scale discriminates the construct assess how well latent to assess how well a single item discriminates the latent construct; $H_{(i)}$ $H_{(ij)}$, scalability coefficient for each pair of items. A set of items

[7] For a review of the MSA, recommend reading Loevinger, 1947; Sijtsma & Molenaar, 2002; Ligtvoet et al., 2010; Sijtsma, et al., 2011; Stochl, et al. 2012.

forms a Mokken scale if all scalability coefficients are greater than 0.3, which was recommended by literature about MSA.

2. ***"Monotonicity"***: to identify items that conform to the monotonic homogeneity model, i.e. the relationship of an item to the overall scale; if the score on an item is high, there is a probability that the overall scale score will be high, thus increasing the levels of the latent construct; after eliminating items that do not meet the criteria for monotonicity, the H coefficients with higher values are considered for item discrimination.
3. Then, after eliminating the items that do not meet the criteria investigated above, is carried outthe ***"Item Invariant Ordering***"(IIO), i.e. the order of difficulty of the items to which the subjects respond, irrespective of their abilities.

The ROC curve procedure was used to identify the best AUC and cut-off; sensitivity, specificity and accuracy were derived from this procedure. In addition, the classification table for the identification of predicted and actual values and logistic regression followed.

A correlation matrix between ACE-III, MMSE, M-ACE, M-ACE6 and GDS was then performed to assess convergent and divergent validity. Welch's test was used to compare the mean scores obtained on the tests between groups.

3.4 Results and discussions

The non-Gaussian distribution of the sample was confirmed (see Tables 4 – 5), with skewness and kurtosis values exceeding the reference values (-1 and +1, -3 and +3), and a significant Shapiro-Wilk test. Levene's test was significant on all ACE-III items, thus suggesting a violation of the assumption of equal variances. Furthermore, the subgroup 'MCI vs. no MCI' was deemed to be too imbalanced for the purposes of further analysis and was therefore excluded from the study. The results of the descriptive analyses are presented in tables 3.

					Shapiro-Wilk	
ITEM	N	Media	Median	SD	W	p
Item1	181	3.177	3	1.610	0.884	<.001
Item2	181	4.033	4	1.021	0.811	<.001
Item3	181	2.917	3	0.363	0.407	<.001
Item4	181	2.099	2	1.774	0.874	<.001
Item5	181	1.657	2	1.157	0.824	<.001
Item6	181	4.613	5	2.086	0.901	<.001
Item7	181	1.475	1	1.352	0.865	<.001
Item8	181	1.833	1	2.213	0.797	<.001
Item9	181	2.011	2	1.543	0.906	<.001
Item10	181	3.210	3	1.961	0.947	<.001
Item11	181	2.840	3	1.749	0.950	<.001
Item12	181	2.657	3	0.702	0.566	<.001
Item13	181	1.528	2	0.822	0.562	<.001
Item 14	181	1.586	2	0.596	0.667	<.001
Item15	181	1.762	2	0.488	0.524	<.001
Item16	181	8.630	10	3.162	0.890	<.001
Item17	181	2.862	3	1.242	0.820	<.001
Item18	181	0.883	1	0.322	0.373	<.001
Item19	181	0.425	0	0.496	0.628	<.001
Item20	181	0.729	0	0.912	0.671	<.001
Item21	181	2.133	1	1.851	0.831	<.001
Item22	181	3.652	4	0.813	0.490	<.001
Item23	181	3.840	4	0.607	0.291	<.001

Tab.4 - Shapiro-Wilk test on the total sample

Asymmetry		Kurtosis	
Asymmetry	IF	Kurtosis	IF
-0.4369	0.181	-1.026	0.359
-1.2371	0.181	1.835	0.359
-2.4592	0.181	10.487	0.359
0.3251	0.181	-1.317	0.359
-0.3243	0.181	-1.344	0.359

-0.5147	0.181	-0.757	0.359
0.4758	0.181	-0.994	0.359
0.9227	0.181	-0.409	0.360
0.4337	0.181	-0.683	0.360
-0.0608	0.181	-0.804	0.359
0.1915	0.181	-0.766	0.359
-2.3281	0.181	5.840	0.359
-1.2507	0.181	-0.335	0.360
-1.1324	0.181	0.279	0.359
-1.9430	0.181	3.034	0.359
-0.6548	0.181	-0.678	0.359
-0.8964	0.181	-0.247	0.359
-2.4083	0.181	3.843	0.360
0.3042	0.181	-1.929	0.359
0.5642	0.181	-1.567	0.359
0.4837	0.181	-1.266	0.359
-2.7881	0.181	8.185	0.359
-4.5772	0.181	22.471	0.359

Tab.5- Asymmetry and kurtosis on the total sample

Considering the distribution's inherent characteristics, Spearman's Rho coefficient was utilised to formulate the correlation matrix encompassing the 23 items of the ACE-III scale. The items exhibited substantial correlations with $p < .001$, exhibiting an association intensity ranging from moderate to strong (0.765 large value, 0.202 small value).

3.4.1 ROC curve and cut-off determination for M-ACE, ACE-III and MMSE

After exploring the nature of the distribution and constructing the correlation was performed, a ROC (Receiver Operating Characteristic) curve analysis both on the total sample “Controls vs Cognitive Decline” and for the different subgroups: “Dementia vs No Dementia”, “MCI vs Dementia”. The optimal cut-

off for the M-ACE, ACE-III and MMSE score. The cut-off was chosen as the point of maximum compromise between sensitivity and specificity. Model performance was also assessed by the area under the curve (AUC), an index expressing the model's ability to discriminate between the two classes. An AUC value of 0.5 indicates random discrimination, while a value close to 1 suggests excellent discrimination ability was determined.

A cut-off of 19.5 is the result for discrimination to “Non-clinical group” vs “Cognitive decline” group; the AUC is 0.939 (sensitivity=0.887, specificity=0.827). From the results obtained from the M-ACE for the “Dementia” vs “No dementia” group, the cut-off identified is 16.5 (sensitivity=0.859, specificity=0.932, AUC=0.947); we then proceed to the analysis on the MCI vs dementia group, identifying a cut-off of 10.5 (sensitivity=0.922, specificity=0.861, AUC=0.944).

The same analyses were performed on ACE-III and MMSE. All results are described in the tables. As already described in the literature, the M-ACE also showed good psychometric qualities in the reference sample, almost on a par with the ACE-III and in some cases better than the MMSE for discriminating subjects with dementia from MCI in the subgroup “MCI vs Dementia”, showing better indices than the MMSE (Tab.6;7;8).

Testing	Cut-off	Sensitivity	Specificity	AUC	Accuracy
M-ACE	**19.5**	**0.887**	**0.827**	**0.939**	**0.862**
ACE-III	68.5	0.952	0.893	0.984	0.928
MMSE	24.5	0.924	0.867	0.964	0.900

Tab.6 - Description of psychometric qualities of tests on the sample "Non-clinical group vs. Cognitive decline".

Testing	Cut-off	Sensitivity	Specificity	AUC	Accuracy
M-ACE	**16.5**	**0.859**	**0.932**	**0.947**	**0.901**
ACE-III	58.5	0.909	0.932	0.982	0.922
MMSE	20.5	0.857	0.883	0.962	0.872

Tab.7- description of psychometric qualities of tests on the sample “Dementia vs. No dementia”

Testing	Cut-off	Sensitivity	Specificity	AUC	Accuracy
M-ACE	**10.5**	**0.922**	**0.861**	**0.944**	**0.900**
ACE-III	51.5	1.00	1.00	1.00	1.00
MMSE	20.5	0.922	0.750	0.930	0.860

Tab.8- description of psychometric qualities of tests on the “MCI vs. Dementia” sample

The logistic regression model was applied to the M-ACE for the various groups in order to examine its predictive validity, with the result that the M-ACE appears to predict MCI discrimination by dementia more effectively than the other groups (Tab.9;10;11). However, it is important to note that certain items

were found to be non-significant, and certain indices, such as deviance and AIC, exhibited high values. This could be attributed to the presence of moderate correlations between the items of the scale, a phenomenon known as multicollinearity. This hypothesis was verified using the Variance Inflation Factor (VIF scores 1< x >5) and the number of observations of one class compared to the other. However, the values were acceptable.

It was hypothesized that the model may not be able to predict the least frequent class.

Model	Deviance	AIC	R^2_{McF}
1	57.1	69.1	0.563

Predictor	Estimate	IF	Z	OR	95% CI	p
Intercept	8.340	1.733	4.814			<.001
item1	-0.855	0.271	-3.150	0.425	[0.251, 0.717]	0.002
item6	-0.721	0.256	-2.812	0.486	[0.294, 0.804]	0.005
item8	-0.157	0.269	-0.584	0.855	[0.503, 1.455]	0.559
item11	-0.735	0.343	-2.144	0.480	[0.247, 0.933]	0.032
item21	-0.843	0.304	-2.770	0.431	0.236, 0.785]	0.006

Tab.9- Logistic regression on M- ACE and "MCI vs Dementia"

Model	Deviance	AIC	R^2_{McF}
1	91.5	103	0.628

Predictor	Estimate	IF	Z	OR	95%CI	p
Intercept	10.415	1.813	5.744			<.001
item1	-0.887	0.246	-3.599	0.412	[0.256, 0.663]	<.001
item6	-0.486	0.188	-2.583	0.615	[0.428, 0.883]	0.010
item8	-0.131	0.148	-0.888	0.877	[0.657, 1.171]	0.374
item11	-1.198	0.267	-4.478	0.302	[0.178, 0.512]	<.001
item21	-0.151	0.164	-0.923	0.860	[0.626, 1.181]	0.356

Tab.10- Logistic regression on M-ACE and "Non-clinical group" vs "Cognitive decline"

Model	Deviance	AIC	R^2_{McF}
1	93.8	106	0.621

Predictor	Estimate	IF	Z	OR	95%CI	p
Intercept	6.684	1.182	5.65			<.001
item 1	-0.488	0.193	-2.53	0.614	[0.424, 0.888]	0.012
item 6	-0.320	0.174	-1.84	0.726	[0.520, 1.015]	0.066
item 8	-0.298	0.171	-1.74	0.742	[0.533, 1.032]	0.082
item 11	-1.189	0.257	-4.62	0.305	[0.183, 0.510]	<.001
item 21	-0.255	0.179	-1.42	0.775	[0.547, 1.099]	0.155

Tab.11- Logistic regression on M-ACE and "Dementia vs no Dementia"

In terms of prediction, confusion matrices (Tab.12) for M-ACE are given below for both the total sample and subgroups.

	Non-clinical group	**Cognitive Decline**
Non-clinical group	62	9
Cognitive Decline	9	101
	MCI	**Dementia**
MCI	31	6
Dementia	10	63
	No Dementia	**Dementia**
No Dementia	98	10
Dementia	6	67

Tab.12- Confusion matrix

From the logistic regression and classification table analyses, the M-ACE can be considered a competitive test. It shows good psychometric qualities for all discriminations of healthy subjects from those with cognitive decline and in subgroups. In particular, it shows higher qualities than the MMSE in the "MCI vs. Dementia" subgroup, suggesting better discriminatory abilities than the latter test in subjects with MCI.

In terms of psychometric indices, the finding of the same cut-off on the MMSE both in the total sample “Non-clinical group vs. Cognitive decline” and in the subgroup “MCI vs. Dementia” also indicates a low sensitivity and specificity of the instrument. The M-ACE also showed higher sensitivity and specificity than the MMSE in the “Dementia vs. No dementia” group. In all groups the ACE-III showed higher psychometric qualities than the M-ACE and the MMSE.

3.4.2 Mokken Scale Analysis (MSA) and logistic regression

The MSA was performed on the 110 subjects in the clinical group. As required by the package, the scores of the different ACE-III items were grouped into ordinal categories that were as homogeneous as possible, and the items were renamed in order to perform the analysis on R (Table 13).

Item1	**Temporal Orientation**
Item2	Spatial Orientation
Item3	Register 3 items
Item4	Subtractions
Item5	Recall 3 items
Item6	Anterograde memory
Item7	Retrograde memory
Item8	Anterograde recall

Item9	Anterograde recognition
Item10	Verbal fluency
Item11	Categorical fluency
Item12	Verbal comprehension
Item13	Writing
Item14	Word repetition
Item15	Sentence repetition
Item16	Name
Item17	Understanding naming
Item18	Reading
Item19	Intersecting figures
Item20	Copy of cube
Item21	Clock Drawing Test
Item22	Points account
Item23	Fragmented letters

Tab.13- Items renamed

From the Mokken analysis, the first results of the H-index suggest the elimination of some ordinal variables, as the H-coefficient is below 0.3 (Table 14, values highlighted). The scaling coefficient of the items of the whole scale is 0.354 (>0.3).

Item	Hi	SE
item1	0.362	(0.050)
item2	0.433	(0.066)
item3	0.348	(0.079)
item4	0.453	(0.047)
item5	**0.260**	**(0.065)**
item6	0.369	(0.051)
item7	**0.298**	**(0.063)**
item8	0.331	(0.057)
item9	**0.279**	**(0.062)**
item10	0.376	(0.056)
item11	0.393	(0.058)
item12	0.315	(0.074)
item13	0.338	(0.064)
item14	**0.266**	**(0.073)**
item15	**0.237**	**(0.093)**
item16	0.451	(0.045)

item17	0.440	(0.051)
item18	0.335	(0.093)
item19	0.332	(0.072)
item20	0.308	(0.073)
item21	0.300	(0.062)
item22	0.413	(0.134)
item23	0.668	(0.065)
coefH scales	0.354	(0.039)

Tab.14- Coefficient H, MSA

The evaluation of the monotonicity of the items was continued. From this analysis, the items "1", "3", "7", "10", "12", "16", "18", "23" were eliminated because the CRIT value, which was not zero (van Schuur, 2011), showed a high number of violations during the analysis, i.e. the items did not fulfil the monotonicity condition,

From this last analysis, the items on which we will continue the MSA analysis are:

"2", "4", "6", "8", "11", "13", "19", "20", "21", "22".

Items that meet the criteria of monotonicity can be examined for item ordering (IIO), which is invariant and necessary for the development of replicable hierarchies across sample responses (Ht=0.610) (Table 15). The resulting scale is then composed as follows:

Item22	**Points account**
Item2	Spatial orientation
Item13	Writing
Item6	Anterograde memory
Item4	Subtractions
Item20	Copy of Cube
Item21	Clock Drawing Test
Item11	Categorical fluency

Item19	Intersecting figures
Item8	Anterograde memory recall

Tab 15- Items of the MSA

For items included in the analysis, the item per domain with the highest coefficients was chosen for clinical and cognitive domain assessment reasons. Some items, such as "spatial orientation" (item2), were chosen at the expense of "subtraction" (item4), as the assessment of orientation is important in patients with cognitive decline, especially in AD and vascular disease, the most common etiological subtypes (Coughlan et al., 2018).

"Intersecting figures" (item 19) and "copying a cube or Necker's cube" (item 20) were chosen over "counting dots" (item 22) to investigate the presence of constructive apraxia, i.e. the inability to plan and execute purposeful movements. Constructive apraxia is a cognitive deficit that is useful for diagnosing cognitive decline, even in its early stages (Chandra et al., 2015); tests for this deficit are included in both the MoCA (Necker's cube) and the MMSE (intersecting pentagons). As for the 'clock design' (item21), although the coefficient is at the limit of acceptability, it was included in the forthcoming analyses because it is recognised as a screening test that correlates well with the MMSE and has shown good reliability. It is generally used to discriminate between healthy and AD subjects. It assesses various cognitive functions, including selective attention, visuospatial ability and executive function (Park et al., 2018).

Item 19 seems to be the most discriminating of the three items relating to visual-spatial skills. A quick calculation of the difficulty of the items using R shows that item 19 has a low mean (1.23) and is therefore more difficult than the other items in the domain.

Once the items have been selected, the MSA is carried out again on the scale obtained in order to study its characteristics. Taking into account the initial coefficients, it was decided to continue on the MSA first on the scale with items 19, 20, 21, whose coefficient was the highest of the three (0.332), and then to add items 20 and 21 in order to study the best conditions of the scale. The scaling coefficients are shown in Table 16.

Item	**H**	**SE**
Item2	0.456	0.09
Item6	0.405	0.06
Item8	0.433	0.08
Item11	0.410	0.08
Item13	0.365	0.07
Item 19	0.320	0.05
coefH	0.438	0.05

Tab16- scalability of items obtained above

It is evident that all items achieve satisfactory values for discrimination within the scale. Furthermore, the scalability coefficient of the full scale exceeds the value of 0.4, thereby indicating the effective scalability of the combination of

items. In addition, the monotonicity and orderability of the items was assessed, resulting in an Ht of 0.81.

The scale, in order of difficulty, should be administered as follows:

	Item	**Domain**
Item2	Spatial orientation	Orientation and attention
Item6	Anterograde memory	Memory
Item13	Writing	Language
Item11	Categorical fluency	Fluency
Item19	Intersecting figures	Visual-spatial skills
Item8	Recall	Memory

Tab.17- M-ACE6

The inclusion of items 20 and 21 did not enhance the scale parameters, and in fact, the coefficients were reduced by several points. The coefficient obtained for item 20 was 0.419, and for item 21, it was 0.393. Following the acquisition of the final version of M-ACE6 from the MSA, a logistic regression was conducted to evaluate the efficacy of the selected model in predicting cognitive decline in the sample and its subgroups. The analysis yielded an R_2 of 0.640 in the "Non-clinical group vs. Cognitive decline" subdivision, with all coefficients being negative. This suggests that higher scores on the items

indicate a lower probability of belonging to the clinical group. The coefficients for items 6 and 8 were not statistically significant, with p values of 0.07 and 0.441, respectively. These items pertain to anterograde memory and the recall of information acquired in the anterograde memory item. It is conceivable that the strong correlation between these two items hinders the discernment of the individual effect of the predictors. The assessment of episodic memory necessitates the administration of both items. Item 19 did not demonstrate statistical significance (-0.944, p=0.1). However, the remaining items (i.e. items 11, 12, and 13) were found to be significant predictors for the regression model (see Table 13;14).

Model	Deviance	AIC	R^2_{McF}
1	88.4	102	0.640

Predictor	Estimate	IF	Z	OR	95% CI	p
Intercept	14.151	2.668	5.305			<.001
item2	-1.315	0.466	-2.823	0.268	[0.107, 0.672]	0.005
item6	-0.377	0.208	-1.813	0.686	[0.457, 1.030]	0.070
item8	-0.116	0.150	-0.771	0.891	[0.662,1.201]	0.441
item11	-1.201	0.273	-4.396	0.301	[0.176, 0.514]	<.001
item13	-1.086	0.528	-2.056	0.338	[0.120, 0.948]	0.040
item19	-0.944	0.574	-1.644	0.389	[0.126, 1.199]	0.100

Tab.13- Logistic regression on M-ACE6 and "Non-clinical group vs Cognitive decline"

	Non-clinical group	**Cognitive Decline**
Non-clinical group	65	6
Cognitive Decline	9	101

Tab.14- Confusion matrix

In the analysis of “MCI vs. Dementia", the R_2 value is found to be low (0.479), and the model's coefficients are generally not optimal. However, items 6, 11, 13, and 19 exhibit significant coefficients, thereby indicating their potential for discriminating between MCI and dementia cases. In this instance, items 2 and 8 were found to be non-significant for the model(Table 15;16).

Model	Deviance	AIC	R^2_{McF}
1	67.7	81.7	0.479

Predictor	Estimate	IF	Z	OR	95% CI	p
Intercept	9.6869	2.364	4.098			<.001
item2	-0.8920	0.477	-1.868	0.410	[0.161, 1.042]	0.062
item13	-0.7920	0.392	-2.021	0.452	[0.210, 0.973]	0.043
item19	-1.6632	0.819	-2.030	0.189	[0.037, 0.962]	0.042
item11	-0.9597	0.296	-3.248	0.383	[0.216, 0.681]	0.001
item6	-0.5857	0.226	-2.587	0.557	[0.356, 0.873]	0.010
item8	-0.0883	0.248	-0.356	0.915	[0.564, 1.486]	0.722

Tab 15- Logistic regression on M-ACE6 and “MCI vs Dementia”

	MCI	Dementia
MCI	29	7
Dementia	6	67

Tab.16- Confusion matrix

Logistic regression analysis was also applied to the “Dementia vs. no Dementia"”group. The R^2 value was found to be 0.656, indicating that 65.6% of the variability in the data could be explained by the model. It was determined that items 2, 11 and 19 were statistically significant for the model (Tab.17;18).

Model	Deviance	AIC	R^2_{McF}
1	85.2	99.2	0.656

Predictor	Estimate	IF	Z	OR	95%CI	p
Intercept	10.044	2.030	4.947			<.001
item2	-0.967	0.414	-2.334	0.380	[0.169, 0.854]	0.020
item6	-0.290	0.182	-1.592	0.748	[0.522, 1.072]	0.111
item8	-0.190	0.195	-0.974	0.827	[0.564,1.213]	0.330
item11	-1.298	0.281	-4.615	0.273	[0.158, 0.470]	<.001
item13	-0.641	0.379	-1.693	0.527	[0.253, 1.098]	0.090
item19	-1.568	0.664	-2.361	0.208	[0.057, 0.762]	0.018

Tab.17- Logistic regression on M-AC E6 and “Dementia vs no dementia”

	No Dementia	**Dementia**
No Dementia	97	11
Dementia	10	63

Tab.18- Confusion matrix

In the groups defined by the variables "Non-clinical group vs. Cognitive decline" and "Dementia vs. No dementia", the model obtained appreciable indices overall. However, in the group defined by the variable "MCI vs. dementia", the model coefficients appear to be inappropriate.

The high deviance observed in the present logistic regression models could be attributed to the the number of observations of one class compared to the other (e.g. MCI=37 subjects, dementia subjects=73), suggesting that the model may lack the capacity to predict the least frequent class.

A comparison of linear logistic regression models reveals that M-ACE6 obtained superior parameters in the groups “Dementia vs. no dementia” and “Non-clinical group vs. Cognitive decline”. For the subgroup “MCI vs. no MCI”, M-ACE slightly better predicts this discrimination.

In order to evaluate the performance of the model in differentiating between “Non-clinical group” and “Cognitive decline”, a 10-fold cross-validation was performed. In this approach, the dataset was divided into 10 subsets of equal size for the purpose of training the model. This process was repeated for all 10 folds, ensuring that each sample was used for both training and validation at least once. The accuracy of the model and other metrics were calculated as the average of the results obtained on each fold.

It is also important to note that no pre-processing of the data, such as normalisation or imputation, was performed prior to cross-validation. The distribution of samples across the various folds was found to be relatively uniform, with a variable number of samples in each fold (172, 171, 172, etc.).

The 10-fold cross-validation results were: average accuracy= 0.899 and Kappa= 0.782.

These results suggest that the model has good predictive capacity. The cross-validation results show that the logistic regression model has robust

performance and that the 10-fold cross-validation has ensured that the model is not over-fitted. The findings indicate that the model exhibited a robust capacity to accurately categorise the samples, exhibiting a substantial concordance between the predicted and actual labels.

The 10-fold cross-validation procedure was also applied to the diagnostic subgroups in order to assess the robustness and generalizability of the model within clinically differentiated samples. Specifically, the analysis was conducted separately for the "Dementia" vs "Non-dementia" (average accuracy=0.895, Kappa=0.787) groups and the "MCI" vs "Dementia" groups (average accuracy=0.832, Kappa=0.62). The validation on the diagnostic subgroups showed good performance for the comparison between dementia and non-dementia, but there is potential for improvement when it comes to classifying between MCI and dementia.

Following the validation of the model's predictivity, the optimal cut-offs for the M-ACE 6 test were determined. As previously undertaken, this was achieved through the implementation of the ROC curve, thereby establishing the cut-offs and indices of sensitivity, specificity, and accuracy for the analyses. For the "Non-clinical group" vs. "Cognitive decline" group, the optimal cut-off is 15.5 (sensitivity=0.934, specificity=0.867, AUC=0.963, accuracy=0.906). For the "Dementia vs. no Dementia" group, the identified cut-off is 13.5 (specificity=0.922, sensitivity=0.872, AUC=0.964, accuracy=0.901).

The following tables show the values of the tests M-ACE, M-ACE6, ACE-III and MMSE to compare the parameters.

Testing	Cut-off	Sensitivity	Specificity	AUC	Accuracy
M-ACE	16.5	0.903	0.898	0.956	0.862
ACE-III	68.5	0.906	0.953	0.961	0.928
MMSE	24.5	0.896	0.782	0.949	0.883
M-ACE6	**15.5**	**0.934**	**0.867**	**0.963**	**0.906**

Tab.19- Comparison of parameters “Non-clinical group” vs “Cognitive Decline”

Testing	Cut-off	Sensitivity	Specificity	AUC	Accuracy
M-ACE	13.5	0.876	0.833	0.939	0.901
ACE-III	58.5	0.913	0.877	0.958	0.922
MMSE	20.5	1.00	0.791	0.945	0.872
M-ACE6	**13.5**	**0.872**	**0.922**	**0.964**	**0.901**

Tab 20- Comparison of parameters Dementia vs no Dementia

Testing	Cut-off	Sensitivity	Specificity	AUC	Accuracy
M-ACE	10.5	0.922	0.861	0.947	0.890
ACE-III	51.5	1.00	1.00	1.00	1.00
MMSE	20.5	0.922	0.750	0.930	0.860
M-ACE6	**9.5**	**0.868**	**0.937**	**0.926**	**0.879**

Tab.21-Comparison of MCI vs Dementia parameters

As demonstrated in the tables, M-ACE6 attains superior parameters in certain instances when compared to the other assessments under consideration. In our sample, M-ACE6 exhibits enhanced sensitivity and specificity in the “Non-clinical group” vs “Cognitive declin” and “Dementia” vs “No dementia” groups when contrasted with M-ACE and MMSE. However, these two parameters demonstrate variability when M-ACE6 is juxtaposed with ACE-III. When comparing MCI to dementia, M-ACE6 demonstrated higher specificity compared to M-ACE and MMSE, lower sensitivity compared to M-ACE, MMSE and ACE-III, yet higher accuracy compared to MMSE. The analysis revealed that M-ACE6 exhibited excellent capabilities in differentiating between healthy subjects and those with cognitive decline (including MCI), with slightly diminished abilities compared to M-ACE in distinguishing between MCI and dementia subjects.

Following the extraction of the indexes of interest, a correlation matrix was constructed in order to evaluate the divergent and convergent validity of M-ACE and M-ACE6 (Tab.22). A correlation matrix with Spearman's R was used as the measurement of validity. For convergent validity, a positive correlation with analogous tests such as ACE-III and MMSE is anticipated. Conversely, divergent validity is indicated by negative correlations with GDS.

The findings revealed that both M-ACE and M-ACE6 exhibited satisfactory convergent validity with the ACE-III and MMSE tests. However, no

correlations were observed with GDS, which measures a distinct construct. Furthermore, all the tests are significantly correlated with the level of education, with the exception of GDS.

		ACE-III	MMSE	M-ACE	M-ACE6	GDS
ACE-III	**Spearman's Rho**	-				
	gdl	-				
	p-value	-				
MMSE	**Spearman's Rho**	0.916***	-			
	gdl	179	-			
	p-value	<.001	-			
M-ACE	**Spearman's Rho**	0.957***	0.901***	-		
	gdl	179	179	-		
	p-value	<.001	<.001	-		
M-ACE6	**Spearman's Rho**	0.957***	0.879***	0.957***	-	
	gdl	179	179	179	-	
	p-value	<.001	<.001	<.001	-	
GDS	**Spearman's Rho**	-0.140	-0.093	-0.128	-0.136	-
	gdl	177	177	177	177	-
	p-value	0.061	0.215	0.087	0.069	-

Tab 22- Correlation matrix ACE-III, MMSE, M-ACE, M-ACE6, GDS and years of education

3.4.3 Welch's test for comparing averages between groups

The means of each group were compared, with the choice of Welch's test as the comparison coefficient being informed by the presence of different variances in the sample, as ascertained by Levene's test (West et al., 2021). The application of the “MCI vs Dementia”, “Dementia vs No Dementia”, “Non-clinical group” vs “Cognitive decline” models resulted in the identification of significant differences between the groups for all three categories. The

utilization of M-ACE, M-ACE6, ACE-III and MMSE tests yielded substantial effect sizes, signifying that the observed variations are not merely random but rather statistically significant. The effect size for the “MCI vs no Dementia” group is larger in M-ACE than in M-ACE6, and slightly larger for the “Non-clinical group” vs “Cognitive decline” and “Dementia” vs “No Dementia” groups. Consequently, it can be concluded that these tests are useful in differentiating between clinical and healthy populations in a clinical or research context(Tab.23;24;25).

		Statistics	p	Average difference	Difference SE		Effect Size
M-ACE	**t of Welch**	15.3	<.001	11.43	0.748	d of Cohen	2.29
M-ACE6	**t of Welch**	15.5	<.001	9.81	0.635	d of Cohen	2.30
ACE-III	**t of Welch**	16.0	<.001	29.76	1.856	d of Cohen	2.34
MMSE	**t of Welch**	18.0	<.001	8.50	0.471	d of Cohen	2.53

Tab.23-Welch's t “Non-clinical group vs. Cognitive decline”

	Statistic		p	Average difference	Difference SE		Effect Size
M-ACE	**t of Welch**	15.5	<.001	11.42	0.735	d of Cohen	2.31
M-ACE 6	**t of Welch**	15.6	<.001	9.86	0.633	d of Cohen	2.32
ACE-III	**t of Welch**	16.5	<.001	31.03	1.877	d of Cohen	2.50
MMSE	**t of Welch**	15.9	<.001	8.72	0.549	d of Cohen	2.47

Tab.24- Welch's t Dementia vs No Dementia

		Statistics	p	Average difference	Differenc e SE		Effect Size
M-ACE	**t of Welch**	10.97	<.001	7.28	0.664	d of Cohen	2.22
M-ACE6	**t of Welch**	8.09	<.001	4.55	0.563	d of Cohen	1.61
ACE-III	**t of Welch**	12.04	<.001	21.86	0.465	d of Cohen	2.
MMSE	**t of Welch**	14.43	<.001	6.72	1.816	d of Cohen	2.34

Tab.25- Welch's t MCI vs Dementia

3.5 General discussion of results

In the present study, the psychometric qualities of the M-ACE were explored by means of the ROC curve and identification of cut-offs. The M-ACE demonstrated good psychometric qualities when compared to the MMSE, but not to the ACE-III, in the subgroups "Non-clinical group vs "Cognitive decline", "MCI vs Dementia", and "Dementia vs No Dementia". The Mokken Scale was utilised to identify the most effective items for discriminating between subjects with pathology and healthy subjects. This approach was selected because the ACE-III questionnaire incorporates ordinal variables, for which the use of the MSA is recommended, and, furthermore, because it is non-parametrically adapted to the sample distribution. The MSA was utilised to derive the M-ACE6, a scale comprising items assessing spatial orientation, anterograde memory, delayed recall, categorical fluency, writing and

visuospatial ability. Logistic regression was employed to evaluate the predictivity of the model, which exhibited notable efficacy across all subgroups of the sample.

The total score attained was 29, with cut-off points established at 15.5 for the "Non- clinical group" vs "Cognitive decline" group, 13.5 for the "Dementia" vs "No dementia" group, and 9.5 for the "MCI" vs "Dementia" group. The instrument's sensitivity appears to be inadequate in detecting early signs of cognitive decline, suggesting that it lacks the capacity to accurately recognise Mild Cognitive Impairment (MCI). The instrument may be more effective in distinguishing healthy subjects from those with decline (cut-off 15.5) than in distinguishing MCI from dementia. The logistic regression model shows good overall performance, with high accuracy and excellent classification ability. The use of 10-fold cross-validation ensured that the model was not overfitted and could generalize well to new data. Validation on the diagnostic subgroups showed good performance for the comparison between dementia and non-dementia, but there is potential for improvement when it comes to classifying between MCI and dementia.

The correlation between the tests used in the study made it possible to assess convergent and divergent validity, with all the cognitive tests showing correlation with each other; the correlation was not present with the GDS questionnaire, which was constructed for the assessment of depressive symptomatology. Therefore, Welch's t with relative indices suggested a

significance in the difference between the group averages. Although the differences found were slight, the M-ACE6 showed a slight superiority in psychometric qualities over the standard version, suggesting that the inclusion of the items “intersecting figures”, “spatial orientation” in place of the “clock drawing test” and “temporal orientation” and the addition of “writing” may improve the test's capacity to differentiate between the clinical population and healthy subjects, subjects with dementia and those without the condition. However, when it comes to discriminating between MCI and dementia, the M-ACE is preferred for slightly better indices. The M-ACE6, an updated version of the Mini-Addenbrooke’s Cognitive Examination, differs significantly from the earlier M-ACE in its improved sensitivity and specificity, indicating greater accuracy in detecting cognitive impairments. Compared to the MMSE, a tool still widely used in clinical practice, the M-ACE6 offers a more comprehensive and sensitive alternative, incorporating items of higher difficulty and a more detailed assessment of cognitive domains that are often overlooked, such as verbal fluency and episodic memory. The findings of the present study support these distinctions, demonstrating higher sensitivity and specificity values for the M-ACE6 compared to both the original M-ACE and the MMSE, further substantiating its diagnostic efficacy.

3.6 Limits and future research

The present study is not without its limitations. Firstly, with regard to the sample size (N=181), the division into groups reduced the number of subjects for the various diagnoses. The sampling in this study is convenience sampling, the limitations of which relate to the generalization of results, as would be the case if the sample were randomized. In practice, however, random sample selection for the target population would be feasible using comprehensive databases of the data to be analysed, but datasets in this field often contain genetic and biological information. Convenience sampling is more commonly used in studies of clinical populations (Andrade et al., 2021). In the present study, no power analysis was conducted, as the sample size was determined by the total number of eligible patients attending the clinic during a defined time period, based on available clinical data. Another potential limitation is the sample size in the MSA. The minimum number of subjects required to perform the analysis is not yet defined.

A sample size estimate set the minimum for Mokken scaling at 400 (Meijer & Baneke, 2001), but sample sizes for articles published with Mokken scaling have been shown to range from 133 to 15.022 (Straat et al., 2014). Watson et al. (2018) state that, at present, it is not yet possible to define the minimum threshold, but that a sample size of 200 subjects might be sufficient for analysis.

However, the recruitment of large numbers of subjects in psychological research is complex, especially when the sample consists of clinical subjects. As far as individuals with MCI are concerned, their small sample size can be considered representative above all in terms of availability; the subject with MCI, in fact, often has difficulty recognising the symptomatology and sometimes even accepting it, implementing an avoidance mechanism of the diagnosis. Concerning the group "MCI vs dementia", the imbalance of number of subjects could reduce the power of the statistical analyses employed.

Broader limitations of the study include the utilization of brief neuropsychological test versions, which are designed to be expeditious. However, these versions must not compromise the accuracy of the results to a significant extent. Reducing the number of items could compromise the diagnostic goodness of the test and reduce the psychometric qualities. In the present study, statistical analyses were conducted that took into account several test parameters, investigating indices such as sensitivity, specificity, AUC and the confusion matrix that returns the comparison between the values predicted by the model and the actual values. Finally, the neuropsychological assessment depends on the administrator and the professional administration and assessment skills.

The neuropsychological assessment is subject to certain rules, including the requirement for a silent environment, the prohibition of assistance to the subject, and the respect of the timing of the administration of specific items. The use of a single administrator, as was the case in this instance, has the

potential to increase the risk of errors during the administration process. Subjective parameters such as a possible reduction in attention towards the end of the day must also be considered. This limitation was addressed through a comparison of cases with the referring neurologist. The continuation of the research work would be advantageous. Initially, the administration of the M-ACE6 should be evaluated in a larger sample, with groups balanced by diagnosis and an appropriate number of cases by etiological subtypes (e.g. AD and FTD). Subsequent investigation should focus on the diagnostic capacity of the test in subjects with MCI, and the study should include a larger team, with more administrators from more outpatient settings. Although the cut-off values obtained from the ROC analysis provide preliminary evidence of the diagnostic utility of the M-ACE6, it is important to consider that demographic factors such as age and education level may influence cognitive performance and, consequently, the validity of fixed cut-off scores across different groups. In the present study, due to the limited sample size, it was not possible to perform separate analyses for subgroups. Future studies with larger and more diverse samples will be needed to assess whether adjustments to the cut-off values based on population characteristics are necessary, in order to enhance diagnostic accuracy. Additionally, it would be worthwhile to make comparisons between the various statistical methods related to the detection of new scales, with a view to providing more precise parameters and results regarding the object of study.

Conclusion

Within the diagnostic context, the neuropsychological assessment of dementia includes screening tests for global cognitive functioning and for specific cognitive functions. Neuropsychological tools are of fundamental importance in clinical practice as they allow early identification of patients at risk, facilitating early interventions that can improve quality of life and slow disease progression.

In particular, tests such as the ACE-III, the M-ACE, the MoCA, and the MMSE are assessment tools that allow the measurement of global cognitive functioning. In addition, ACE-III and M-ACE return domain scores, providing the clinician with additional information useful for diagnostic purposes. The present study aimed to obtain normative data of the M-ACE in an Italian sample of subjects with MCI and dementia. There is currently only one study in Italy that has investigated its psychometric characteristics on a sample of patients with HIV dementia, an aetiological subtype characterised by motor difficulties and thought disorders (Trunfio et al., 2022). The parameters analysed returned good sensitivity and specificity for the reference sample. The same consideration can be pronounced for the version obtained in the present study, the M-ACE6, consisting of 6 items investigating spatial orientation, anterograde memory, delayed recall, categorical fluency, writing and visual-

spatial abilities. Using non-parametric statistical analyses, it was possible to analyse their predictive, convergent and divergent validity; the ROC curve was constructed for each subgroup and the AUC was analysed. The M-ACE6 is a good test for assessing dementia and for discriminating between those with cognitive decline and healthy individuals. In the MCI versus dementia group, the M-ACE6 showed slightly lower performance than the M-ACE.

Neuropsychological testing research plays an important role in the field of neurodegenerative diseases. In addition to being fundamental in the clinical field, testing plays an equally fundamental role in research. One thinks of all those studies of all disciplines (medical, biological, genetic) that have made use of them. Another function of tests is that of follow-ups. Both in the clinical field, to understand the worsening or stability of patients, and in the scientific field to compare studies and make them homogeneous.

In the follow-up to this research work, the aim was to follow a methodological procedure as appropriate as possible in order to provide scientifically approvable data. The “intervening variables” were always lurking, but it was ensured that this work was approvable and reliable, presenting both results that were significant for the original objectives and results that did not fulfil the intentions.

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APPENDIX

M-ACE ITALIAN VERSION

MINI ADDENBROOKE'S COGNITIVE EXAMINATION - M-ACE
Versione italiana

nome:	data del test:…./……/……..	
data di nascita:	somministratore……	
	anni di scolarità…….	
ospedale:	occupazione……	
	preferenza manuale……	

ATTENZIONE- Orientamento

	chiedere	giorno	data	mese	anno	stagione	**Attenzione** [Punti 0-4]
		……..	……..	……	…….	…….	

MEMORIA

Dire "Adesso leggerò un nome e un indirizzo che lei dovrà ripetere dopo di me. Faremo in questo modo per 3 volte, così avrà l'opportunità di impararlo. Più tardi glielo chiederò di nuovo"

Calcolare solo il punteggio del terzo trial.

Memoria [Punti 0-7]

	I trial	II trial	III trial
Mario Rossetti	…….. ……..	…….. ……..	…….. ……..
Piazza Garibaldi 59	….. ……. ….	….. ……. ….	….. ……. ….
Pontedera	…….	…….	…….
Pisa	……	……	……

FLUENZA VERBALE – Animali

Animali

Ora dovrebbe dirmi il nome di più animali possibile, che iniziano con qualsiasi lettera. Ha un minuto di tempo"

Fluenza
[Punti 0-7]

					>21	7
					17-21	6
					14-16	5
					11-13	4
					9-10	3
					7-8	2
					5-6	1
					<5	0
					totale	corrette

ABILITA' VISUO-SPAZIALI - Test dell'orologio

Orologio: chiedere al soggetto di disegnare il quadrante di un orologio con i numeri e le lancette alle undici e dieci. (Per il punteggio guardare le istruzioni sulla guida: cerchio=1; numeri=2; lancette=2 se sono tutti corretti)

Visuospazial
[Punti 0-5]

MEMORIA - Richiamo

Chiedere: “Ora mi dica ciò che si ricorda di quel nome e di quell’ indirizzo che abbiamo ripetuto all’inizio” Mario Rossetti …… …….. Piazza Garibaldi 59 ……. …… …….. Pontedera …….. Pisa ……..	**Memoria** [Punti 0-7]
PUNTEGGIO TOTALE	**/30**

M-ACE6 ITALIAN VERSION

MINI ADDENBROOKE’S COGNITIVE EXAMINATION – M-ACE6
Versione italiana 6 item

nome: data di nascita: ospedale:	data del test:…./……/…….. somministratore…… anni di scolarità……. occupazione…… preferenza manuale……

ATTENZIONE- Orientamento

chiedere	luogo	piano	città	regione	stato	**Attenzione** [Punti 0-5]
	……	……	……	……	……	

MEMORIA - Anterograda

Dire “Adesso leggerò un nome e un indirizzo che lei dovrà ripetere dopo di me. Faremo in questo modo per 3 volte, così avrà l’opportunità di impararlo. Più tardi glielo chiederò di nuovo”
Calcolare solo il punteggio del terzo trial.

Memoria [Punti 0-7] ☐

	I trial	II trial	III trial
Mario Rossetti	…….. ……..	…… ……	…… ……
Piazza Garibaldi 59	….. ……. ….	…. ……. ….	…. ……. ….
Pontedera	……	……	……
Pisa	……	……	……

LINGUAGGIO - Scrittura

Dire: “Vorrei che scrivesse due frasi. Può scrivere quello che vuole. Dovrà però scrivere delle frasi di senso compiuto senza utilizzare abbreviazioni”. Se il soggetto non sa che scrivere, l’esaminatore potrà suggerire qualche argomento dicendo: “Per esempio, potrebbe scrivere qualcosa sulla sua ultima vacanza, su ciò che fa nel tempo libero, sulla sua famiglia o i suoi figli”. Se il soggetto scrive solo una frase, allora ricordare di scriverne un’altra.

Le frasi devono contenere soggetto e verbo. Ortografia e grammatica debbono essere considerate. Le frasi non devono necessariamente riguardare lo stesso argomento.

Linguaggio
[Punti 0-2]

FLUENZA VERBALE – Animali

Animali

Ora dovrebbe dirmi il nome di più animali possibile, che iniziano con qualsiasi lettera. Ha un minuto di tempo”

Fluenza
[Punti 0-7]

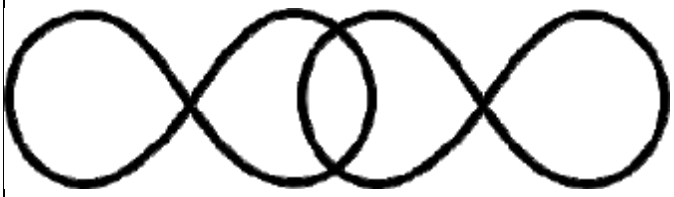
>21	7
17-21	6
14-16	5
11-13	4
9-10	3
7-8	2
5-6	1
<5	0
totale	corrette

ABILITA’ VISUO-SPAZIALI - Copia disegni e test dell’orologio

Pentagoni sovrapposti: chiedere al soggetto di copiare questa figura:

(il punto si assegna se le figure si intersecano e non vengono disegnati cerchi uniti)

Visuospaziale
[Punti 0-1]



MEMORIA - Richiamo

Chiedere: “Ora mi dica ciò che si ricorda di quel nome e di quell’ indirizzo che abbiamo ripetuto all’inizio”

Mario Rossetti Piazza Garibaldi 59 dera Pisa	…… …….. ……. …… …….. …….. ……..

Memoria
[Punti 0-7]

PUNTEGGIO GENERALE **/29**

Acknowledgments

OMISSIS